APPENDIX A

MICHIGAN SUPREME COURT
LANSING, MICHIGAN

[Filed March 29, 2005]

SC: 124284
COA: 238549
Oakland CC: 01-029676-CZ

HASTINGS MUTUAL INSURANCE CO.,
Plaintiff-Appellee/Cross-Appellee,

v.

KELLY SCOTT RUNDELL, QUENTIN MERLD RUNDELL, SR., PATRICIA RUNDELL, and QUENTIN MERLD RUNDELL, JR.,
Defendants/Cross-Appellants,

and

SHIRLEY GWEN HUNTER and JAMES FLYNN HUNTER,
Defendants-Appellants.

ORDER

On order of the Court, the motion for reconsideration of this Court's order of December 27, 2004 is considered, and it is DENIED, because it does not appear that the order was entered erroneously.

[Logo]

I, CORBIN R. DAVIS, Clerk of the Michigan Supreme Court, certify that the foregoing is a true and complete copy of the order entered at the direction of the Court.

March 29, 2005

/s/ Alvin R. Davis
ALVIN R. DAVIS
Clerk

APPENDIX B

MICHIGAN SUPREME COURT
LANSING, MICHIGAN

[Filed December 27, 2004]

SC: 124284
COA: 238549
Oakland CC: 01-029676-CZ

HASTINGS MUTUAL INSURANCE CO.,
Plaintiff-Appellee,

v.

KELLY SCOTT RUNDELL, QUENTIN MERLD RUNDELL, SR., PATRICIA RUNDELL, and QUENTIN MERLD RUNDELL, JR.,
Defendants/Cross-Appellants,

and

SHIRLEY GWEN HUNTER and JAMES FLYNN HUNTER,
Defendants-Appellants/ Cross-Appellants.

ORDER

By order of January 29, 2004, the application for leave to appeal the July 1, 2003 judgment of the Court of Appeals, and the application for leave to appeal as cross-appellants, were held in abeyance pending the decision in *Allstate Insurance Company v McCarn (After Remand)* (Docket No. 122849). On order of the Court, the opinion having been issued on July 30, 2004, 471 Mich 283 (2004), the applications are again considered, and they are DENIED, because we are not persuaded that the questions presented should be reviewed by this Court.

[Logo]

I, CORBIN R. DAVIS, Clerk of the Michigan Supreme Court, certify that the foregoing is a true and complete copy of the order entered at the direction of the Court.

December 27, 2004

/s/ [Illegible]
[Illegible]
Clerk

APPENDIX C

STATE OF MICHIGAN COURT OF APPEALS

UNPUBLISHED

[Filed July 1, 2003]

No. 238549
Oakland Circuit Court
LC No. 01-029676-CZ

HASTINGS MUTUAL INSURANCE CO.,
Plaintiff-Appellee/Cross-Appellee,

v.

KELLY SCOTT RUNDELL, QUENTIN MERLD RUNDELL, SR., PATRICIA RUNDELL, and QUENTIN MERLD RUNDELL, JR.,
Defendants-Appellants/Cross-Appellants,

and

SHIRLEY GWEN HUNTER and JAMES FLYNN HUNTER,
Defendants-Appellants.

Before: CAVANAGH, P.J., and GAGE and ZAHRA, *JJ.*

PER CURIAM.

Defendants appeal as of right the trial court's order granting plaintiff's motion for summary disposition. We affirm.

I. Factual and Procedural History

Defendants Quentin Merld Rundell, Sr. ("Quentin Sr."), and his wife, Patricia Rundell. ("Patricia"), had a homeowners' insurance policy with plaintiff. Their son, Kelly Scott Rundell ("Kelly"), lived with them at the time. As a resident relative, Kelly was an insured under the policy. On Sep-

tember 9, 1998, Kelly was seen driving a car in the parking lot of Davisburg Medical Center. He was steering the car with one hand and had his other hand on a shotgun, which was resting on the sill of the car and was pointed out the window of the car. He stopped the car, got out, and walked toward the entrance of Davisburg Medical Center with the shotgun under his jacket. When he was in front of the entrance, defendant Shirley Gwen Hunter ("Shirley") was walking out the front door. Shirley held the door open so that Kelly could grab it and walk through. However, instead of walking through the door, Kelly stopped walking and stood in front of Shirley. Shirley then stepped to get out of Kelly's way. A witness saw Kelly raise his arm and then heard three shots. Shirley fell to the ground after being shot in the buttock and pretended to be unconscious. Kelly looked at her, kicked her foot, and laughed. He then turned around, walked back to the car, and drove away. Later, doctors told Shirley that she had been shot twice. However, medical records show that she had one entrance wound and one exit wound. Kelly was later apprehended at his home, where police found a sawed-off shotgun. Inside a car parked at the home, police found a pipe-cutter and the barrel of the shotgun that had been cut off. Kelly was evaluated at the Center for Forensic Psychiatry ("Forensic Center") and was diagnosed with schizophrenia.[1]

Shirley and her husband, James Flynn Hunter (collectively, "the Hunter defendants"), filed a lawsuit against Kelly, Quentin Sr., Patricia, Quentin Merld Rundell, Jr. ("Quentin

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[1] Kelly was charged with assault with intent to murder, MCL 750.83, three counts of possession of a firearm during the commission of a felony, MCL 750.227b, possession of a short-barreled shotgun/rifle, MCL 750.224b, carrying a concealed weapon, MCL 750.227, felonious assault, MCL 750.82, and resisting and obstructing a police officer, MCL 750.479. The trial court determined that Kelly was incompetent to stand trial and dismissed the charges against him. This Court affirmed. *People v Rundell*, unpublished opinion per curiam of the Court of Appeals, issued 11/20/01 (Docket No. 232459).

Jr.") (collectively, "the Rundell defendants"), and Davisburg Medical Center, Inc., to recover damages for the shotgun injuries to Shirley (referred to as "the underlying action").[2] Plaintiff later filed the complaint against defendants in the present case, seeking a declaratory judgment that it had no duty to defend or indemnify and had no liability under the insurance policy for the Hunters' claims of injury in the underlying action.[3] On November 28, 2001, the trial court issued an opinion and order granting plaintiff's motion for summary disposition under MCR 2.116(0). The trial court concluded that Shirley's injuries were not covered under the policy because: (1) there was no question of fact that the shooting was not an accident and was therefore not an "occurrence" pursuant to the policy, (2) the policy's intentional acts exclusion to coverage applied because Shirley's injuries were the natural and foreseeable consequences of Kelly's intentional act, (3) Kelly's mental illness did not alter the conclusion that his actions were intentional, and (4) the deriva-

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[2] The Hunter defendants made the following claims in the underlying action: (1) premises liability against Davisburg Medical Center, Inc., (2) negligent storage and/or disposal of a firearm against Quentin Sr. and Patricia, who lived with Kelly and stored the shotgun he used to shoot Shirley in their home, (3) negligent storage and/or disposal of a firearm against Quentin Jr., who owned the shotgun Kelly used to shoot Shirley, (4) negligent discharge of a firearm against Kelly, (5) battery against Kelly, (6) nuisance against Davisburg Medical Center, Inc., and (7) loss of companionship and society against the Rundell defendants and Davisburg Medical Center, Inc.

[3] Plaintiff had filed a similar complaint against defendants in 2000. However, plaintiff voluntarily dismissed the case without prejudice after the trial court denied its motion for summary disposition and set the case for trial. The trial court denied plaintiff's motion for summary disposition after determining that there were "genuine issues of material fact regarding whether Kelly Rundell acted either intentionally or criminally and whether, in his mental condition, he reasonably expected or actually intended that the injury would result."

tive negligent conduct is excluded from coverage because it derived from an act that was excluded by the policy.

II. Analysis

A. Standard of Review

Plaintiff filed its motion for summary disposition pursuant to MCR 2.116(C)(10).

> A motion for summary disposition under MCR 2.116 (C)(10) tests the factual sufficiency of the complaint. *Veenstra v Washtenaw Country Club*, 466 Mich 155, 163; 645 NW2d 643 (2002). A motion for summary disposition should be granted when, except in regard to the amount of damages, there is no genuine issue in regard to any material fact and the moving party is entitled to judgment or partial judgment as a matter of law. MCR 2.116(C)(10), (G)(4); *Veenstra, supra* at 164. In deciding a motion brought under this subsection, the trial court must consider affidavits, pleadings, depositions, admissions, and other evidence submitted by the parties, MCR. 2.116(G)(5), in a light most favorable to the nonmoving party. *Veenstra, supra* at 164. . . . The decision whether to grant a motion for summary disposition is a question of law that is reviewed de novo. *Id.* at 159. [*Kelly-Stehney & Assoc, Inc v MacDonald's Industrial Products, Inc*, 254 Mich App 608, 611-612; 658 NW2d 494 (2003).]

Similarly, issues involving the proper interpretation and application of an insurance contract are reviewed de novo. *Cohen v Auto Club Ins Ass'n*, 463 Mich 525, 528; 620 NW2d 840 (2001). In reviewing an insurance policy, we first look to the language of the policy and interpret its terms in accordance with the principles of contract construction. *Allstate Ins Co v McCarn*, 466 Mich 277, 280; 645 NW2d 20 (2002). An insurance policy must be enforced according to its terms. *Id.* If the terms are not defined by the policy, they are given their

commonly used meanings. *Id.* A term is not rendered ambiguous by the fact that the policy does not define the term. *Henderson v State Farm Fire & Casualty Co*, 460 Mich 348, 354; 596 NW2d 190 (1999), if the teams of the policy are ambiguous, we construe the policy in favor of the insured. *Id.* However, where the terms of the policy are unambiguous, the policy must be enforced as written. *Id.*

B. The Intentional Acts Exclusion

Defendants argue that the trial court erred in concluding as a matter of law that Kelly's shooting of Shirley was not an accident or "occurrence"[4] and fell within the intentional acts exclusion of the policy. Assuming, without deciding, that defendants are correct that the trial court erred in concluding that the shooting was an "occurrence" as a matter of law, we conclude that the trial court did not err in determining as a matter of law that the intentional acts exclusionary clause in the policy was applicable. The intentional acts exclusionary clause of the policy provides, "Medical payments to others do not apply to 'bodily injury' or 'property damage' . . . which may reasonably be expected to result from the intentional or criminal acts of an 'insured' or which is in fact intended by an 'insured.' "*In Allstate Ins Co v Judith Miller* (After Remand), 226 Mich App 574, 581-582; 575 NW2d 11. (1997), this Court analyzed a substantially similar policy exclusion:

> The language "reasonably be expected" is unambiguous and requires that the court apply an objective standard of expectation. *[Allstate Ins Co v] Freeman*, [432 Mich 656, 686; 443 NW2d 734 (1989).] By contrast, the language "in fact intended by an insured

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[4] According to the language of the policy, liability coverage for damages arises from an "occurrence." The policy defines an "occurrence" as "an accident, including continuous or repeated exposure to substantially the same general harmful conditions," which results in bodily injury or property damage.

person" requires that the court apply a subjective standard of expectation. *See id.* Thus, coverage is excluded under the policy when (1) the insured acted either intentionally or criminally and (2) the insured either reasonably expected or actually intended that the particular injury would result from his intentional or criminal conduct. An injury is reasonably expected where it is the natural, foreseeable, expected, and anticipated result of the intentional or criminal conduct. *Id.* at 687-688.

In regard to the first prong of the analysis, defendants argue that there is a question of fact regarding whether the shooting was intentional. In support of this argument, defendants argue that Kelly stated at the Forensic Center that the shooting was an accident and that he did not mean to hurt anyone. However, we can find nothing in the Forensic Center records submitted by defendants supporting this claim. While in the Forensic Center, Kelly gave various accounts of the incident. At times he denied any involvement in the shooting, denied being present at the scene of the shooting, and denied owning a gun. At other times, he admitted owning a gun and admitted being present at a bank near the scene of the shooting. On one occasion, he stated, "I just got back from depositing two checks and I went for a walk, with the shotgun. And I went off and hit Mrs. Hunter. That's about it" Kelly's statement that "I went off' does not support the contention that the gun discharged accidentally. Despite defendants' allegation, there is no evidence that Kelly ever indicated that the shooting was unintentional. Kelly never gave any sworn testimony regarding the shooting and will not testify about the shooting at any trial because the lower court found that Kelly was mentally incompetent to testify at trial. The other evidence submitted includes deposition testimony that one of the witnesses saw Kelly raise his arm and heard the shotgun go off. Shirley was shot in the buttock, fell to the ground, and pretended like she was unconscious. Kelly kicked Shirley's unmoving body, laughed, walked back to his

car, and drove away. In light of this evidence, we conclude that there is no question of material fact that Kelly fired the gun intentionally.

Defendants also argue that, even if Kelly did not mistakenly shoot the gun, he did not have the mental capacity to expect or intend that the injury would result from his conduct. Kelly was diagnosed with schizophrenia. The criminal charges filed against Kelly were dismissed because he was found incompetent to stand trial. However, Kelly's mental illness is not relevant to whether the shooting was an intentional act under the policy. It is significant that the facts surrounding the insured's role in the shooting are viewed from an objective perspective. "[W]hile an insane or mentally ill insured may be unable to form the criminal intent necessary to be charged with murder, such an individual can still intend or expect the results of the injuries he causes." *Auto-Owners Ins Co v Churchman*, 440 Mich 560, 563; 489 NW2d 431 (1992). "[W]hen the evidence unequivocally shows that the insured intended his or her actions, the existence of mental illness does not alter that conclusion." *Dale Miller v Farm Bureau Mut Ins Co*, 218 Mich App 221, 234; 553 NW2d 371 (1996). "[T]he law in Michigan is clear. Evidence that an insured suffers from mental illness, standing alone, does not create a genuine issue of material fact regarding whether the insured intended his actions or the consequences of his actions." *Id.* at 231. It is improper for a court to determine that, because there is evidence of the insured's mental incapacity, a factual question exists in regard to whether the insured acted intentionally. *Judith Miller*, *supra* at 582.

We conclude that Shirley's injury was a natural, foreseeable, expected, and anticipated result of Kelly's conduct. A person who fires a sawed-off shotgun from close range toward a person at the entrance of a public building may reasonably expect that it is highly likely that injury or death

will result from such actions. The fact that Kelly was mentally ill at the time of the shooting does not alter the conclusion that he intended to shoot the gun and that a reasonable person could expect that injury would result from the shooting. Therefore, the trial court did not err in determining that the intentional act exclusion applies in this case.

C. Schizophrenia as a Physical Disability

Defendant Kelly argues that the trial court erred in failing to hold that he was physically disabled due to his schizophrenia. However, the trial court in fact entered an order declaring that Kelly "lacks sufficient physical or mental capacity or sense of obligation to testify truthfully and understandably in a civil deposition or civil trial . . . . " In support of this argument, Kelly argues that "[t]he 400 year[-]old archaic common law rule that the insane person is strictly liable for his torts and must perform to the level of an ordinary reasonable person must be reversed." Kelly goes into an in-depth analysis of the nature of schizophrenia and quotes several cases that describe expert's testimony regarding mental illness, but does not explain how his arguments relate to the present case or why the trial court erred in granting summary disposition. "Insufficiently briefed issues are deemed abandoned on appeal." *Etefia v Credit Technologies, Inc*, 245 Mich App 466, 471; 628 NW2d 577 (2001). Therefore, Kelly has not properly presented this issue for appeal.

D. Constitutional Arguments

Kelly also argues that requiring him "to perform to the level of the ordinary reasonable man" violates the Equal Protection Clauses of the United States and Michigan Constitutions, US Const, Am XIV; Const 1963, art 1, §2, the Due Process Clauses of the United States and Michigan Constitutions, US Const, Am XIV; Const 1963, art 1, §17, and the cruel and unusual punishment clauses of the United States and Michigan Constitutions, US Const, Am VIII;

Const 1963, art 1, §16. Kelly argues that requiring him to perform at the level of an ordinary person "is requiring an impossibility and is an uncivilized law." Kelly then presents several public policy reasons why mentally ill people like himself should not be required to perform at the level of an ordinary person. Kelly also argues that SJI 13.03 regarding mental illness "is uncivilized and violates the equal protection, due process, and cruel and inhuman punishment provisions of the Michigan and United States Constitutions" and "must be reversed."

Kelly does not expand on his arguments or give any valid legal support for his arguments. The only cases Kelly cites merely stand for general principles of law.[5] "'A party may not merely announce a position and leave it to this Court to discover and rationalize the basis for the claim.'" *Eldred v Ziny*, 246 Mich App 142, 150; 631 NW2d 748 (2001), quoting *In re Webb H Coe Marital & Residuary Trusts*, 233 Mich App 525, 537; 593 NW2d 190 (1999). "[T]his Court need not address an issue that is given only cursory consideration by a party on appeal." *Eldred, supra* at 150. Because this issue was not properly presented for appeal, we decline to address this issue.[6]

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[5] Kelly cites *Neal v Oakwood Hosp Corp*, 226 Mich App 701, 716; 575 NW2d 68 (1997) for the proposition that "[b]oth the federal and state constitutions provide that no person will de denied the equal protection of the law." He also cites *Lake Michigan College Federation of Teachers v Lake Michigan Community College*, 518 F2d 1091, 1094 (1975), cert den 427 US 904; 96 S Ct 3189; 49 L Ed 2d 1197 (1976), for the proposition that "[t]he safeguards of procedural due process apply only when a person is deprived of liberty or property . . ." Finally, he cites *Cooperative Fire Ins Ass'n v Combs*, 648 A2d 857, 860 (Vt, 1994), where the Vermont Supreme Court joined the jurisdictions that had held "that as a matter of law an insane person is to be considered incapable of forming an intent to cause injury."

[6] Furthermore, we note that in regard to this issue, the Supreme Court did not flatly hold that mentally ill people are held to the standard of an

III. Conclusion

We conclude that there is no question of material fact that Kelly's act of shooting the shotgun was an intentional act that caused an injury that could reasonably be expected to result from his act. Therefore, the trial court did not err in determining that the intentional acts exclusion to the policy applies and that plaintiff is relieved of its obligation to indemnify or defend against the insureds. Accordingly, the trial court did not err in granting plaintiff's motion for summary disposition.

Affirmed.

/s/ Mark J. Cavanagh
/s/ Hilda R. Gage
/s/ Brian K. Zahra

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ordinary person in all situations. In *Churchman*, *supra* at 563, the Supreme Court held that "while an insane or mentally ill insured may be unable to form the criminal intent necessary to be charged with murder, such an individual can still intend or expect the results of the injuries he causes." "A decision of the Supreme Court is binding upon this Court until the Supreme Court overrules itself . . . ." *O'Dess v Grand Trunk Western Railroad Co*, 218 Mich App 694, 700; 555 NW2d 261 (1996).

APPENDIX D

STATE OF MICHIGAN IN THE CIRCUIT COURT
FOR THE COUNTY OF OAKLAND

[Filed Nov. 28, 2001]

Case No: 01-029676-CZ
Hon. Denise Langford Morris

HASTINGS MUTUAL INSURANCE,
Plaintiff,

v.

KELLY SCOTT RUNDELL, *et al.*,
Defendant.

SUMMARY DISPOSITION OPINION AND ORDER

The instant Motion for Summary Disposition was filed by Plaintiff. The Court, being familiar with the facts and after reviewing the Briefs and Exhibits is pursuant to MCR 2.119 (E)(2), dispensing with oral argument and having considered the merits and being fully advised in the premises, now issues its Opinion and Order.

FACTS

This action arises from a shooting which occurred in September of 1998. Kelly Scott Rundell shot Shirley Hunter with a sawed-off shotgun at the Davisburg Medical Center. As a result of the shooting, Shirley Hunter suffered extensive injuries including the loss of and damage to internal organs, permanent disfigurement and scarring and permanent nerve damage to her leg. In November of 1999, Shirley Hunter and her husband brought an action against Kelly Scott Rundell and his family (hereinafter the Rundell Defendants) and Davisburg Medical Center, seeking damages for the injuries suffered as a result of the shooting. The Rundell Defendants

tendered the defense of the underlying action to Hastings Mutual Insurance Company under a homeowner's policy issued to Kelly Scott Rundell's parents. Plaintiff Hastings Mutual brought the instant action seeking a declaratory judgment that it had no duty to defend or indemnify and that coverage does not exist with respect to any claim made in the underlying action.

STANDARD OF REVIEW

MCR 2.116 (C)(10) provides for summary disposition if there is no genuine issue of material fact. Affidavits, pleadings, depositions, admissions or other documentary evidence must be submitted to support or oppose a (C)(10) motion. MCR 2.116 (G)(4). *Quinto v Cross & Peters Co*, 451 Mich 358(1996). In presenting its motion, the moving Party has the initial burden of supporting its position by documentary evidence. The burden then shifts to the opposing party to establish that a genuine issue of disputed fact exists. If the opposing party fails to present documentary evidence establishing the existence of a material factual dispute, the motion is properly granted. *Smith v Globe Life Insurance Co*, 460 Mich 446(1999). The reviewing court should evaluate a (C)(10) Motion by considering the substantively admissible evidence actually proffered in opposition to the motion. A reviewing court may not employ a standard citing the mere possibility that the claim might be supported by evidence produced at trial. *Maiden v Rozwood*, 461 Mich 109(1999).

ANALYSIS

The policy defines the term "occurrence" as an accident. However, the policy does not define "accident". In *Frankenmuth Mutual v Masters*, 460 Mich 105, 114(1999), the Michigan Supreme Court held that the term "accident" is not ambiguous and means "an undesigned contingency, a casualty, a happening by chance, something out of the usual

course of things, unusual, fortuitous, not anticipated and not naturally to be expected." The testimony of the witnesses confirms that after driving through the parking lot of the Davisburg Medical Center with the weapon pointing out of the driver's side window. Kelly Scott Rundell parked, exited the vehicle and walked toward the building with the shotgun concealed under his jacket, which was draped over his arm. He approached Shirley Hunter as she was leaving the building. Kelly Scott Rundell walked past Shirley Hunter and the shotgun discharged. There is a dispute over how many shots were fired. One shot entered the buttocks and exited her abdomen. While Shirley Hunter was on the ground, Kelly Scott Rundell kicked her foot and laughed. He then walked away and went around a corner. He got into the vehicle and drove away while being chased by Kevin Sendi. (Michael Sanford Deposition, pp 15, 16, 20-25; Lola Stover Deposition, p 8-__, 18-22; Shirley Hunter Deposition, p 2__. Kelly Scott Rundell has been declared incompetent to testify. However, he has made conflicting statements regarding the incident, including an assertion that the gun discharged accidentally.

The Court finds that the facts presented in this case demonstrate that the shooting was not an accident. There is no dispute that Kelly Scott Rundell carried the shotgun from the vehicle. There is no dispute that the shotgun was loaded. That the loaded shotgun discharged and hit someone cannot be characterized as an undesigned contingency. Therefore, the Court finds that the shooting incident is not an occurrence pursuant to the policy.

In addition, the Court finds that the intentional acts exclusion of the policy is applicable. The policy excludes coverage for bodily injuries that are reasonably expected from the intentional acts of an insured. The only evidence necessary for the exclusion to apply is evidence demonstrating that the injuries were the natural result of an intentional act. Michigan Courts have held that an insured, even if insane, can reasonably foresee the consequences of intentional acts.

In *Miller v Farm Bureau Ins*, 218 Mich App 221, 234(1996), the court stated, "when the evidence unequivocally shows that the insured intended his or her actions, the existence of mental illness does not alter that conclusion." The Michigan Supreme Court confirmed that mental illness will not impact the decision en whether an intentional acts exclusion is applicable to deny coverage in *Allstate Insurance v Freeman*, 432 Mich 656, 686(1989). This Court finds that the facts presented in this case demonstrate that the injuries inflicted on Shirley Hunter were the natural and foreseeable consequences of an intentional act.

Finally, the Court finds that the derivative negligent conduct alleged is also excluded. The Court must consider the underlying cause of the injury to determine coverage. The underlying cause of the injuries arose from excluded act, therefore any duty of the insurer is derivative and thus also excluded. *Allstate Insurance v Johnson*, 205 Mich App 495(1994). There is no coverage for the intentional acts of Kelly Scott Rundell. The basis for the damage claims arises out of an excluded act. Because the claims against the Rundell Defendants are derivative of an excluded act, there can be no coverage under the policy for the negligence claims raised against those Defendants.

Accordingly,

IT IS IIEREBY ORDERED that Plaintiff-Hastings Mutual Insurance Company's Motion for Summary Disposition pursuant to MCR 2.116(C)(10) is GRANTED.

This resolves the last pending claim and closes the case.

IT IS SO ORDERED.

Dated: Nov. 28, 2001.

/s/ Judge Denise Langford Morris
DENISE LANGFORD MORRIS
Circuit Court Judge

APPENDIX E

DIAGNOSTIC AND STATISTICAL MANUAL
OF MENTAL DISORDERS

FOURTH EDITION
TEXT REVISION

DSM-IV-TR tm

AMERICAN PSYCHIATRIC ASSOCIATION

2000

Page XXX Introduction

"DEFINITION OF MENTAL DISORDER

Although this volume is titled. the DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, the term mental disorder unfortunately implies a distinction between 'mental' disorders and 'physical' disorders that is a reductionistic anachronism of mind/body dualism. A compelling literature documents that there is much 'physical' in 'mental' disorders and much 'mental' in 'physical' disorders. The problem raised by the term 'mental' disorders has been much clearer than its solution, and, unfortunately, the term persists in the title of DSM-IV because we have not found an appropriate substitute."

APPENDIX F

LEGITIMATING BRAIN DISEASE: The Case Against "Mental Illness"

The following is based on an article by Enid Peschel, PhD (deceased) and Richard Peschel, MD, PhD, of the Yale University School of Medicine in The Journal of the California AMI.

Schizophrenia, schizoaffective disorder, bipolar and major depressive disorders, autism, pervasive developmental disorders, obsessive compulsive disorder, Tourette's disorder, anxiety and panic disorders, and attention deficit hyperactivity disorder are physical brain disorders. Scientifically verifiable abnormalities in brain anatomy, brain chemistry, and brain function help explain these disorders. Computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans show the abnormalities in the brain.

These revolutionary advances in neuroscience require a revolution in language. It's time to get rid of the language of the past and start using accurate, non judgmental, medical terms to describe these brain disorders. It's time to connect these disorders to the affected organ: the brain. Disorders of the nerve cells or neurons of the brain should becalled Neurological Brain Disorders (NBD). This designation puts brain disorders where they belong: in the brain.

The brain is an organ of the body just like any other, only infinitely more complex. And, like the kidneys, lungs, or heart, the brain can malfunction. Language colors and defines how people react to other human beings, things, and illnesses. Think, for example, of the different information conveyed when you say or hear:

A QUACK or A PHYSICIAN

DEMONIC POSSESSION or SEIZURE DISORDER

MENTAL ILLNESS or NEUROBIOLOGICAL DISORDER

"Mental illness" is non-scientific, judgmental, and prejudicial. Not only is it time to use the term NBD for all the physical disorders of the brain, it's also time to re-name some of the NBD's that have confusing or stigmatizing connotations.

Schizophrenia is an example. Because this word is overlaid with so much prejudice, fear, and misunderstanding (varying from associations of madness, violence, dangerousness, and "split personality"), its time to use a new term for this collection of thought disorders. Because its not known yet which regions of the brain are most important in this disease, it would be premature to name it after a specific brain region or malfunction. However, medical disorders are sometimes named for the person who first described them: for example, Alzheimer's disease, Parkinson's disease, Down's syndrome, Tourette's disorder. Thus, schizophrenia could be renamed Kraepelin's disorder (KD) in honor of the doctor who first described it, Emil Kraepelin (1856-1926).

Many civil rights movements have shown that changes in social consciousness cannot occur unless there is a corresponding change in the language used to refer to oppressed groups. Language promotes change. Language is a powerful instrument of justice or an injustice. Let's work together so that, by the year 2,000, the ugly words "mentally ill" will be a thing of the past.

This article has been posted by D.J. Jaffe of the Alliance for the Mentally Ill/Friends and Advocates of the Mentally Ill in NYC.

In April, 1997 new guidelines for the treatment of the brain disease schizophrenia were published by the American Psychiatry Association. Click here for more information on these guideline: First Publication of Practice Guidelines for the Treatment of Patients with Schizophrenia.

APPENDIX G

BRIEFING PAPER

SCHIZOPHRENIA AND MANIC-DEPRESSIVE DISORDER ARE DISEASES OF THE BRAIN

It has been suspected for over a century that schizophrenia and manic-depressive disorder (bipolar disorder) are diseases of the brain. In 1837, Dr. W.A.F. Browne, the best-known English psychiatrist of his generation, wrote:

> Insanity, then, is inordinate or irregular, or impaired action of the mind, of the instincts, sentiments, intellectual, or perceptive powers, depending upon and produced by an organic change in the brain.

In that same year, Dr. Amariah Brigham, one of the founders of American psychiatry, also wrote that insanity "is now considered a physical disorder, a disease of the brain."

It would be 150 years, however, before these statements could be proven. Since the early 1980s, with the availability of brain imaging techniques and other developments in neuroscience, the evidence has become overwhelming that schizophrenia and manic-depressive disorder are diseases of the brain, just as multiple sclerosis, Parkinson's disease, and Alzheimer's disease are diseases of the brain. The brains of individuals with these diseases are measurably different from individuals who do not have these diseases, both structurally and functionally. A brief summary of some of the evidence that proves this point follows.

- Individuals with schizophrenia and manic-depressive disorder, including those who have never been treated, have enlarged ventricles in the brain, as demonstrated in over 100 studies to date.

  Van Horn JD, McManus IC. Ventricular enlargement in schizophrenia A meta-analysis of studies of the

ventricle: brain ratio (VBR) *British Journal of Psychiatry* 160:687-697, 1992.

Soares JC, Mann JJ The anatomy of mood disorders: review of structural neuroimaging studies. *Biological Psychiatry* 41:86-106, 1997.

Elkis H. Friedman L. Wise A, et al. Meta-analyses of studies of ventricular enlargement and cortical sulcal prominence in mood disorders. Comparisons with controls or patients with schizophrenia. *Archives of General Psychiatry* 52:735-746, 1995.

- Individuals with schizophrenia, including those who have never been treated, have a reduced volume of gray matter in the brain, especially in the temporal and frontal lobes.

Lawrie SM, Abukmeil SS: Brain abnormality in schizophrenia: a systematic and quantitative review of volumetric magnetic resonance imaging studies *British Journal of Psychiatry* 172:110-120, 1998.

- Individuals with manic-depressive disorder have an enlarged amygdala and increased numbers of white matter hyperintensities.

Strakowski SM, DelBello MP, Sax KW, et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder *Archives of General Psychiatry* 56:254-260, 1999.

Dupont RM, Jernigan TL, Heindel W, et al. Magnetic resonance imaging and mood disorders localization of white matter and other subcortical abnormalities, *Archives of General Psychiatry* 52:747-755, 1995.

Videbech P. MRI findings in patients with affective disorder: a meta-analysis. *Acta Psychiatrica Scandinavica* 96:157-168, 1997.

- Individuals with schizophrenia and manic-depressive disorder, including those who have never been treated, have more neurological abnormalities, as shown in over 25 studies.

  Schroder J. et al. Neurological soft signs in schizophrenia. *Schizophrenia Research* 6:25-30, 1992.

  Torrey EF, *et al. Schizophrenia and Manic-Depressive Disorder*. New York: Basic Books, 1994, pp. 127 ff. and pp. 176-177.

- Individuals with schizophrenia and manic-depressive disorder, including those who have never been treated, have more neuropsychological abnormalities that impair their cognitive function, including such things as information processing and verbal memory.

  Goldberg TE, Gold JM. Neurocognitive functioning in patients with schizophrenia: an overview. In: *Psychopharmacology: The Fourth Generation of Progress*, Bloom FE and Kupfer DJ (eds). New York: Raven Press, 1995, pp. 1245-1257.

  Hoff AL, Shukla S. Aronson T. *et al.* Failure to differentiate bipolar disorder from schizophrenia on measures of neuropsychological function. *Schizophrenia Research* 3:253-260, 1990.

  Morice R. Cognitive inflexibility and pre-frontal dysfunction in schizophrenia and mania. *British Journal of Psychiatry* 157:50-54, 1990.

- Individuals with schizophrenia, including those who have never been treated, show decreased function of the prefrontal area, an area of the brain that we use for planning and thinking about ourselves.

  Berman KF, Weinberger DR. Functional localization in the brain in schizophrenia. In: *Review of Psychiatry, vol. 10*, Tasman A and Goldfinger S (eds).

Washington DC: American Psychiatric Press, 1991, pp. 24-59.

Andreasen NC, et al. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. *Archives of General Psychiatry* 49:943-958, 1992.

- Approximately 50 percent of individuals with schizophrenia and manic-depressive disorder, including those who have never been treated, have impaired awareness of their own illness. This has been shown in at least 50 different studies. Such individuals do not realize that they are sick, and they will, therefore, usually not accept treatment voluntarily. Studies suggest that this impaired awareness is probably related to the decreased function of the prefrontal area. These individuals are thus similar to some patients who have had a stroke and, because of brain damage, are unaware of their disability and deny it. The lack of awareness of illness in individuals with schizophrenia and manic-depressive disorder is the most common reason that they do not take their medication.

Amador XF, David AS. *Insight and Psychosis*, New York: Oxford, 1998.

Ghaemi SN, Insight and psychiatric disorders: a review of the literature, with a focus on its clinical relevance for bipolar disorder. *Psychiatric Annals* 27:782-790, 1997.

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APPENDIX H

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FOURTH EDITION

TEXT REVISION
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AMERICAN PSYCHIATRIC ASSOCIATION
2000

SCHIZOPHRENIA, pages 298-302

DIAGNOSTIC CRITERIA FOR SCHIZOPHRENIA, pages 312-317

Schizophrenia

The essential features of Schizophrenia are a mixture of characteristic signs and symptoms (both positive and negative) that have been present for a significant portion of time during a 1-month period (or for a shorter time if successfully treated), with some signs of the disorder persisting for at least 6 months (Criteria A and C). These signs and symptoms are associated with marked social or occupational dysfunction (Criterion B). The disturbance is not better accounted for by Schizoaffective Disorder or a Mood Disorder With Psychotic Features and is not due to the direct physiological effects of a substance or a general medical condition (Criteria D and E). In individuals with a previous diagnosis of Autistic Disorder (or another Pervasive Developmental Disorder), the additional diagnosis of Schizophrenia is warranted only if prominent delusions or hallucinations are present for at least a month (Criterion H). The characteristic symptoms of Schizophrenia involve a range of cognitive and emotional dysfunctions that include perception, inferential thinking, language and communication, behavioral monitoring, affect, fluency

and productivity of thought and speech, hedonic capacity, volition and drive; and attention. No single symptom is pathognomonic of Schizophrenia; the diagnosis involves the recognition of a constellation of signs and symptoms associated with impaired occupational or social functioning.

Characteristic symptoms (Criterion A) may be conceptualized as falling into two broad categories: positive and negative. The positive symptoms appear to reflect an excess or distortion of normal functions, whereas the negative symptoms appear to reflect a diminution or loss of normal functions. The positive symptoms (Criteria A1-A4) include distortions in thought content (delusions), perception (hallucinations), language and thought process (disorganized speech), and self-monitoring of behavior (grossly disorganized or catatonic behavior). These positive symptoms may comprise two distinct dimensions, which may in turn be related to different underlying neural mechanisms and clinical correlates. The "psychotic dimension" includes delusions and hallucinations, whereas the "disorganization dimension" includes disorganized speech and behavior. Negative symptoms (Criterion A5) include restrictions in the range and intensity of emotional expression (affective flattening), in the fluency and productivity of thought and speech (alogia), and in the initiation of goal-directed behavior (avolition).

Delusions (Criterion A1) are erroneous beliefs that usually involve a misinterpretation of perceptions or experiences. Their content may include a variety of themes (e.g., persecutory, referential, somatic, religious, or grandiose). Persecutory delusions are most common the person believes he or she is being tormented, followed, tricked, spied on, or ridiculed. Referential delusions are also common; the person believes that certain gestures, comments, passages from books, newspapers, song lyrics, or other environmental cues are specifically directed at him or her. The distinction. Be-

tween a delusion and a strongly held idea is sometimes difficult to make and depends in part on the degree of conviction with which the belief is held despite clear contradictory evidence regarding its veracity.

Although bizarre delusions are considered to be especially characteristic of Schizophrenia, "bizarreness" may be difficult to judge, especially across different cultures. Delusions are deemed bizarre if they are clearly implausible and not understandable and do not derive from ordinary life experiences. An example of a bizarre delusion is a person's belief that a stranger has removed, his or her internal organs and has replaced them with someone else's organs without leaving any wounds or scars. An example of a nonbizarre delusion is a person's false belief that he or she is under surveillance by the police. Delusions that express a loss of control over mind or body are generally considered to be bizarre; these include a person's belief that his or her thoughts have been taken away by some outside force ("thought withdrawal"), that alien thoughts have been put into his or her mind ("thought insertion"), or that his or her body or actions are being acted on or manipulated by some outside force ("delusions of control"). If the delusions are judged to be bizarre, only this single symptom is needed to satisfy Criterion A for Schizophrenia.

Hallucinations (Criterion A2) may occur in any sensory modality (e.g., auditory, visual, olfactory, gustatory, and tactile), but auditory hallucinations are by far the most common, Auditory hallucinations are usually experienced as voices, whether familiar or unfamiliar, that are perceived as distinct from the person's own thought, The hallucinations must occur in the context of a clear sensorium; those that occur while falling asleep (hypnagogic) or waking up (hypnopompic) are considered to be within the range of normal experience. Isolated experiences of hearing one's name called or experiences that lack the quality of an external percept

(e.g., a humming in one's head) should also not be considered as symptomatic of Schizophrenia or any other Psychotic Disorder. Hallucinations may be a normal part of religious experience in certain cultural contexts. Certain types of auditory hallucinations (i.e., two or more voices conversing with one another or voices maintaining a running commentary on the person's thoughts or behavior) have been considered to be particularly characteristic of Schizophrenia. If these types of hallucinations are present, then only this single symptom is needed to satisfy Criterion A.

Disorganized thinking ("formal thought disorder") has been argued by some to be the single most important feature of Schizophrenia. Because of the difficulty inherent in developing an objective definition of "thought disorder," and because in a clinical setting inferences about thought are based primarily on the individual's speech, the concept of disorganized speech (Criterion A3) has been emphasized in the definition for Schizophrenia used in this manual. The speech of individuals with Schizophrenia may be disorganized in a variety of ways. The person may slip off the track" from one topic to another ("derailment" or "loose associations"); answers to questions may be obliquely related or completely unrelated ("tangentiality"); and, rarely, speech may be so severely disorganized that it is nearly incomprehensible and resembles receptive aphasia in its linguistic disorganization ("incoherence" or "word salad"). Because mildly disorganized speech is common and nonspecific, the symptom must be severe enough to substantially impair effective communication. Less severe disorganized thinking or speech may occur during the prodromal and residual periods of Schizophrenia (see Criterion C).

Grossly disorganized behavior (Criterion A4) may manifest itself in a variety of ways, ranging from childlike silliness to unpredictable agitation. Problems may be noted in any form of goal-directed behavior, leading to difficulties in performing-activities of daily living such as preparing a meal or

maintaining hygiene. The person may appear markedly dishevelled, may dress in an unusual manner (e.g., wearing multiple overcoats, scarves, and gloves on a hot day), or may display clearly inappropriate sexual behavior (e.g., public masturbation) or unpredictable and untriggered agitation (e.g., shouting or swearing). Care should he taken not to apply this criterion too broadly. For example, a few instances of restless, angry, or agitated behavior should not be considered to be evidence of Schizophrenia, especially if the motivation is understandable

Catatonic motor behaviors (Criterion A4) include a marked decrease in reactivity to the environment, sometimes reaching an extreme degree of complete unawareness (catatonic rigidity), maintaining a rigid posture and resisting efforts to be moved (catatonic rigidity), active resistance to instructions or attempts to be moved (catatonic negativism), the assumption of inappropriate or bizarre postures (catatonic posturing), or purposeless and unstimulated excessive motor activity (catatonic excitement). Although catatonia has historically been associated with Schizophrenia, the clinician should keep in mind that catatonic symptoms are nonspecific and may occur in other mental disorders (see Mood Disorders With Catatonic Features, p. 417), in general medical conditions (see Catatonic Disorder Due to a General Medical Condition, p. 185), and Medication-Induced Movement Disorders (see Neuroleptic-Induced Parkinsonism, p. 792).

The negative symptoms of Schizophrenia (Criterion A5) account for a substantial degree of the morbidity associated with the disorder. Three negative symptoms—affective flattening, alogia, and avolition—are included in the definition of Schizophrenia; other negative symptoms (e.g., anhedonia) are noted in the "Associated Features and Disorders" section below. Affective flattening is especially common and is characterized by the person's face appearing immobile and unresponsive, with poor eye contact and re-

duced body language. Althpugh a person with affective flattening may smile and warm up occasionally, his or her range of emotional expressiveness is clearly diminished most of the time. It may be useful to observe the person interacting with peers to determine whether affective flattening is sufficiently persistent to meet the criterion. Alogia (poverty of speech) is manifested by brief, laconic, empty replies. The individual with alogia appears to have a diminution of thoughts that is reflected in decreased fluency and productivity of speech. This must be differentiated from an unwillingness to speak, a clinical judgment that may require observation over time and in a variety of situations. Avolition is characterized by an inability to initiate and persist in goal-directed activities. The person may sit for long periods of time and show little interest in participating in work or social activities.

Although common in Schizophrenia, negative symptoms are difficult to evaluate because they occur on a continuum with normality, are relatively nonspecific, and may be due to a variety of other factors (including positive symptoms, medication side effects, depression, environmental understimulation, or demoralization). If a negative symptom is judged to be clearly attributable to any of these factors, then it should not be considered in making the diagnosis of Schizophrenia. For example, the behavior of an individual who has the delusional belief that he will be in danger if he leaves his room or talks to anyone may mimic social isolation, avolition, and alogia. Certain antipsychotic medications often produce extrapyramidal side effects, such as bradykinesia, that may mimic affective flattening. The distinction between true negative symptoms and medication side effects often depends on clinical judgment concerning the type of antipsychotic medication, the effects of anticholinergic medications, and dosage adjustments. The difficult distinction between negative symptoms and depressive symptoms may be informed by the other accompanying

symptoms that are present and the fact that individuals with symptoms of depression typically experience an intensely painful affect, whereas those with Schizophrenia have a diminution or emptiness of affect. Finally, chronic environmental understimulation or demoralization may result in learned apathy and avolition. In establishing the presence of negative symptoms that are to be used in making the diagnosis of Schizophrenia, perhaps the best test is their persistence for a considerable period of time despite efforts directed at resolving each of the potential causes described above. It has been suggested that enduring negative symptoms that are not attributable to the secondary causes described above be referred to as "deficit" symptoms.

Criterion A for Schizophrenia requires that at least two of the five items be present concurrently for much of at least 1 month. However, if delusions are bizarre or hallucinations involve "voices commenting" or "voices conversing," then the presence of only one item is required. The presence of this relatively severe constellation of signs and symptoms is referred to as the "active phase." In those situations in which the active-phase symptoms remit within a month in response to treatment, Criterion A can still be considered to have been met if the clinician judges that the symptoms would have persisted for a month in the absence of effective treatment. In children, evaluation of the characteristic symptoms should include due consideration of the presence of other disorders or developmental difficulties. For example, the disorganized speech in a child with a Communication Disorder should not count toward a diagnosis of Schizophrenia unless the degree of disorganization is significantly greater than would be expected on the basis of the Communication Disorder alone.

Schizophrenia involves dysfunction in one or more major areas of functioning (e.g., interpersonal relations, work or education, or self-care) (Criterion B). Typically, functioning is clearly below that which had been achieved before the

onset of symptoms. If the disturbance begins, in childhood or adolescence, however, there may be a failure to achieve what would have been expected for the individual rather than a deterioration in functioning. Comparing the individual with unaffected siblings may be helpful in malting this determination. Educational progress is frequently disrupted, and the individual may be able to finish school. Many individuals are unable to hold a job for sustained periods of time and are employed at a lower level than their parents ("downward drift"). The majority (60%-70%) of individuals with Schizophrenia do not marry, and most have relatively limited social contacts. The dysfunction persists for a substantial period 'during the course of the disorder and does not appear to be a direct result of any single feature. For example, if a woman quits her job because of the circumscribed delusion that her boss is trying to kill her, this alone is not sufficient evidence for this criterion unless there is a more pervasive pattern of difficulties (usually in multiple domains of functioning).

Some signs of the disturbance must persist for a continuous period of at least 6 months (Criterion C). During that time period, there must be at least 1 month of symptoms (or less than 1 month if symptoms are successfully treated) that meet Criterion A of Schizophrenia (the active phase). Prodromal symptoms are often present prior to the active phase, and residual symptoms may follow it. Some prodromal and residual symptoms are relatively mild or subthreshold forms of the positive symptoms specified in Criterion A. Individuals may express variety of unusual or odd beliefs that are not of delusional proportions (e.g., ideas of reference or magical thinking); they may have unusual perceptual experiences (e.g., sensing the presence of an unseen person or force in the absence of formed hallucinations); their speech may be generally understandable but digressive, vague, or overly abstract or concrete; and their behavior may he peculiar but not grossly disorganized (e.g., mumbling to themselves, col-

lecting odd and apparently worthless objects). In addition to these positive like symptoms, negative symptoms are particularly common in the prodromal and residual phases and can often be quite severe. Individuals who had been socially active may become withdrawn; they lose interest in previously pleasurable activities; they may become less talkative and inquisitive; and they may, spend the bulk of their time in bed. Such negative symptoms are often the first sign to the family that something is wrong; family members may ultimately report that they experienced the individual as "gradually slipping away."

Diagnostic Criteria for Schizophrenia

A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

(1) delusions

(2) hallucinations

(3) disorganized speech (e.g., frequent derailment or incoherence)

(4) grossly disorganized or catatonic behavior

(5) negative symptoms, i.e., affective flattening, alogia, or avolition

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B. *Social/occupational dysfunction*: For a significant portion of the time since the on-set of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when

the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or occupational achievement).

C. *Duration*: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and Mood Disorder exclusion*: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion*: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. *Relationship to a Pervasive Developmental Disorder*: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Classification of longitudinal course (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms):

Episodic With Interepisode Residual Symptoms (episodes are defined by the reemergence of prominent psychotic symptoms); also specify if: With Prominent Negative Symptoms

Episodic With No Interepisode Residual Symptoms

Continuous (prominent psychotic symptoms are present throughout the period of observation); also specify if: With Prominent Negative Symptoms

Single Episode In Partial Remission; *also specify* if: With Prominent Negative Symptoms

Single Episode In Full Remission

Other or Unspecified Pattern

Schizophrenia Subtypes

The subtypes of Schizophrenia are defined by the predominant symptomatology at the time of evaluation. Although the prognostic and treatment implications of the subtypes are variable, the Paranoid and Disorganized Types tend to be the least and most severe, respectively. The diagnosis of a particular subtype is based on the clinical picture that occasioned the most recent evaluation or admission to clinical care and may therefore change over time. Not infrequently, the presentation may include symptoms that are characteristic of more than one subtype. The choice among sub-types depends on the following algorithm: Catatonic Type is assigned whenever prominent catatonic symptoms are present (regardless of the presence of other symptoms); Disorganized Type is assigned whenever disorganized speech and behavior and flat or inappropriate affect are prominent (unless Catatonic Type is also present); Paranoid Type is assigned whenever there is a preoccupation with delusions or

frequent hallucinations are prominent (unless the Catatonic or Disorganized Type is present). Undifferentiated Type is a residual category describing presentations that include prominent active-phase symptoms not meeting criteria 'or the Catatonic, Disorganized, or Paranoid Type; and Residual Type is for presentations in which there is continuing evidence of the disturbance, but the criteria for the active-phase symptoms are no longer met.

Because of the limited value of the schizophrenia subtypes in clinical and research settings (e.g., prediction of course, treatment response, correlates of illness), alternative subtyping schemes are being actively investigated. The alternative with the most empirical support to date proposes that three dimensions of psychopathology (psychotic, disorganized, and negative) may come together in different ways among individuals with Schizophrenia, This dimensional alternative is described in Appendix B (p.765).

295.30 Paranoid Type

The essential feature of the Paranoid Type of Schizophrenia is the presence of prominent delusions or auditory hallucinations in the context of a relative preservation of cognitive functioning and affect. Symptoms characteristic of the Disorganized and Catatonic Types (e.g., disorganized speech, flat or inappropriate affect, catatonic or disorganized behavior) are not prominent. Delusions are typically persecutory or grandiose, or both, but delusions with other themes (e.g., jealousy, religiosity, or somatization) may also occur. The delusions may be multiple, but are usually organized around a coherent theme. Hallucinations are also typically related to the content of the delusional theme. Associated features include anxiety, anger, aloofness, and argumentativeness. The individual may have a superior and patronizing manner and either a stilted, formal quality or extreme intensity in interpersonal interactions. The persecutory themes may predispose the individual to suicidal

behavior, and the combination of persecutory and grandiose delusions with anger may predispose the individual to violence. Onset tends to be later in life than the other types of Schizophrenia, and the distinguishing characteristics may be more stable over time. These individuals usually show little or no impairment on neuropsychological or other cognitive testing. Some evidence suggests that the prognosis for the Paranoid Type may be considerably better than for the other types of Schizophrenia, particularly with regard to occupational functioning and capacity for independent living.

Diagnostic criteria for 29530 Paranoid Type

A type of Schizophrenia in which the following criteria are met:

A. Preoccupation with one or more delusions or frequent auditory hallucinations.

B. None of the following is prominent: disorganized speech, disorganized or catatonic behavior, or flat or inappropriate affect.

295.10 Disorganized Type

The essential features of the Disorganized Type of Schizophrenia are disorganized speech, disorganized behavior, and flat or inappropriate affect, The disorganized speech may be accompanied by silliness and. laughter that are not closely related to the content of the speech. The behavioral disorganization (i.e., lack of goal orientation) may lead to severe disruption in the ability to perform activities of daily living (e.g., showering, dressing, or preparing meals). Criteria for the Catatonic Type of Schizophrenia are not met, and delusions or hallucinations, if present, are fragmentary and not organized into a coherent theme. Associated features include grimacing, mannerisms, and other oddities of behavior. Impaired performance may be noted on a variety of neuro-

psychological and cognitive tests. This subtype is also usually associated with poor premorbid personality, early and insidious onset, and a continuous course without significant remissions. Historically, and in other classification systems this type is termed *hebephrenic*.

Diagnostic criteria for 295.10 Disorganized Type

A type of Schizophrenia In which the following criteria are met:

A. All of the following are prominent:

(1) disorganized speech

(2) disorganized behavior

(3) flat or inappropriate affect

B. The criteria are not met for Catatonic Type.

295.20 Catatonic Type

The essential feature of the Catatonic Type of Schizophrenia is a marked psychmotor disturbance that may involve motoric immobility, excessive motor activity, extreme negativism, mutism, peculiarities of voluntary movement, echolalia, or echopraxia. Motoric immobility may be manifested by catalepsy (waxy flexibility) or stupor. The excessive motor activity is apparently purposeless and is not influenced by external stimuli. There may be extreme negativism that is manifested by the maintenance of a rigid posture against attempts to be moved or resistance to all instructions. Peculiarities of voluntary movement are manifested by the voluntary assumption of inappropriate or bizarre postures or by prominent grimacing. Echolalia is the pathological, parrotlike, and apparently senseless repetition of a word or phrase just spoken by another person. Echopraxia is the repetitive irritation of the movements of another person. Additional features include stereotypes, and mannerisms, and

automatic obedience or mimicry. During severe catatonic stupor or excitement, the person may need careful supervision to avoid self-harm or harming others. There are potential risks from malnutrition, exhaustion, hyperpyrexia, or self-inflicted injury. To diagnose this subtype, the individual's presentation must first meet the full criteria for Schizophrenia and not be better accounted for by another etiology: substance induced (e.g., Neuroleptic-Induced Parkinsonism, see p. 792), a general medical condition (see p. 185), or a Manic or Major Depressive Episode (see p. 417).

Diagnostic criteria for 295.20 Catatonic Type

A type of Schizophrenia in which the clinical picture is dominated by at least two of the following:

(1) motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor

(2) excessive motor activity (that is apparently purposeless and not influenced by external stimuli)

(3) extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism

(4) peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing

(5) echolalia or echopraxia

295.90 Undifferentiated Type

The essential feature or the Undifferentiated type of Schizophrenia is the presence of symptoms that meet Crite-

rion A of Schizophrenia but that do not meet criteria or the Paranoid, Disorganized, or Catatonic Type.

Diagnostic criteria for 295.90 Undifferentiated Type

A type of Schizophrenia in which symptoms that meet Criterion A are present, but the criteria are not met for the Paranoid, Disorganized, or Catatonic Type.

295.60 Residual Type

The Residual Type of Schizophrenia should be used when there has been. at least one episode of Schizophrenia, but the current clinical picture is without prominent positive psychotic symptoms (e.g., delusions, hallucinations, disorganized speech or behavior). There is continuing evidence of the disturbance as indicated by the presence of negative symptoms (e.g.. flat affect, poverty of speech, or avolition) or two or more attenuated positive symptoms (e.g., eccentric behavior, mildly disorganized speech, or odd beliefs). If delusions or hallucinations are present, they are not prominent and are not accompanied by strong affect. The course of the Residual Type may be time limited and represent a transition between a full-blown episode and complete remission. However, it mav also be continuously present for Many years, with or without acute exacerbations.

Diagnostic criteria for 295.60 Residual Type

A type of Schizophrenia in which the following criteria are met:

A. Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior.

B. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in Criterion A for Schizophrenia, present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

APPENDIX I

KAPLAN & SADDOCK'S COMPREHENSIVE
TEXTBOOK OF PSYCHIATRY
VOLUME I
EIGHTH EDITION
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NEUROIMAGING IN SCHIZOPHRENIA: LINKING NEUROPSYCHIATRIC MANIFESTATIONS TO NEUROBIOLOGY, pages 1396-1407

Raquel E. Gur, M.D., Ph.D., and Ruben C. Gur, Ph.D.

The severe behavioral manifestations of schizophrenia have continued to provide an impetus for efforts at understanding the neurobiology of this complex disorder. Advances in neuroimaging have reached a point at which the convergence of evidence permits several conclusions that link clinical features of schizophrenia to dysfunctional brain systems. Noteworthy advances bridge between clinical and basic neuroscience research, address mechanisms underlying schizophrenia, and have implications for treatment. The contribution of neuroimaging to this effort has been to document abnormalities in whole brain, as well as regional, morphology and physiology in a way that serves to integrate clinical, neurobehavioral, and basic research. In the 5 years since the previous edition of this textbook, the literature on neuroimaging in schizophrenia has nearly doubled compared to the literature that has been available since the inception of imaging in the late 1970s. Clearly, it is impossible to update all aspects of neuroimaging in schizophrenia. Instead, this chapter will highlight the main findings, focusing on the integration of brain and behavior.

As the field of neuroimaging has evolved, complementary progress has also been made in behavioral neurosciences. Such progress includes the development and application of

more precise and efficient measures of neurobehavioral domains, the incorporation of emotion processing and olfaction as probes of limbic function, and improved transitions between human and animal paradigms. There is an increased recognition that schizophrenia is characterized by selective cognitive, emotive, and olfactory processing deficits, against a background of global impairment. The nature of the deficit and findings of impaired performance in unaffected family members have contributed to a shift from examining the genetics of diagnostic categories to a focus on endophenotypic markers, with parallel paradigms in humans and animals. Such work opens the way to the application of microarray technology in genetic analyses and the study of cellular and molecular abnormalities in diverse brain regions. Considered jointly, these advances establish firm foundations for hypothesis-driven research that systematically examines core neurobiological abnormalities underlying schizophrenia. The integration of neurobehavioral and neuroimaging paradigms, essential for functional neuroanatomical investigations, also makes it possible to address fundamental questions. Growing evidence indicates that abnormalities in brain development play formative roles in the pathophysiology of schizophrenia. Examination of neuroleptic-naive, first-episode patients in neurobehavioral and neuroimaging studies helps evaluate the presence of abnormalities at disease onset. Repeated measures can longitudinally address questions regarding disease progression. This section will first present a summary of neurobehavioral studies that provide the probe to brain systems that underlie the disorder and then highlight neuroimaging studies across diverse methods.

The diversity of methods reflects, to some extent, the complexity of the brain and schizophrenia. It is perhaps useful to highlight the main classes of neuroimaging methods in the context of the cascade leading from brain to behavior. The cascade begins at the anatomical substrate and proceeds through the initiation of electrical pulses triggering neuro-

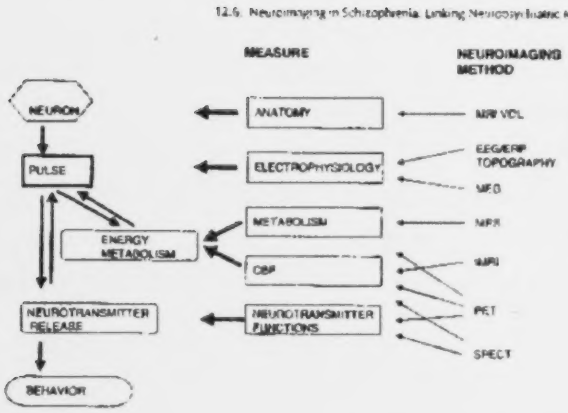
transmitter release, a process that eventuates in relaying the signal for action (Fig. 12.6-1). The process requires energy metabolism. Although far from the cellular level, neuroimaging methods can yield information on every step in this cascade. Magnetic resonance imaging (MRI) technologies can provide morphometric parameters of neuroanatomy. Event-related electrophysiological methods (electroencephalograph), [EEG]/event-related potential [ERP]), based on surface electrodes, as well as magnetoencephalography (MEG), yield information on activity of neuronal aggregates with high temporal and improving spatial resolution. Metabolic biochemical activity can be measured with magnetic resonance spectroscopy (MRS), and functional MRI (fMRI) yields measures of cerebral blood flow (CBF) change. Positron emission tomography (PET) provides functional measures of oxygen and glucose metabolism and of CBF, as well as measures of neurotransmitter function. Single photon emission computed tomography (SPECT) can also evaluate both CBF and receptor function. Together, they afford an impressive arsenal for assessing and studying brain structure and function. New methods are being developed, such as MRI sequences sensitive to the direction and degree of proton diffusion. Because diffusion is greatest along the axonal axis, tensor diffusion imaging (TDI) can trace neuronal fiber tracts, enabling a transition from volumetric measures to tracing connectivity.

NEUROBEHAVIORAL DEFICITS IN SCHIZOPHRENIA

The clinical presentation of schizophrenia is associated with a range of behavioral changes and aberrations that do not directly constitute a part of the clinical characterization but are, nonetheless, salient and crippling. These deficits cover a broad range of behavior, including cognition, emotion, and sensory domains. Understanding the nature and contributions of these impairments is essential for developing models of neural systems involved in schizophrenia.

Cognition. Impaired cognition in schizophrenia, leading to early conceptualizations of "dementia praecox," was well supported by numerous applications of psychological measures. Earlier studies commonly focused on single domains, such as attention, and did not associate cognitive aberrations with functional brain systems. Neuropsychological batteries, which have been initially developed and applied in neurological populations, attempt to link behavioral deficits to brain function. This line of research in schizophrenia, with diverse test batteries, has consistently indicated diffuse dysfunction related to frontotemporal systems, with relatively greater impairment in executive functions and in learning and memory.

Examination of cognition in relation to clinical status has advanced understanding of the nature and scope of impairment in schizophrenia. Two lines of research have been particularly useful in the efforts: the evaluation of new-onset patients and longitudinal follow-up. Neurocognitive deficits are evident at initial clinical presentation, before treatment initiation. Therefore, studying new-onset patients avoids confounding due to the possible consequences of treatment, hospitalization, and social isolation that may contribute to compromised function. Furthermore, it has been observed in longitudinal studies that the cognitive deficits do not show appreciable amelioration with symptomatic relief associated with treatment. However, some neurocognitive domains have improved with treatment, perhaps more so with atypical neuroleptics: Yet, methodological issues limit conclusions, as most studies applied typical neuroleptics in a relatively high dose. Furthermore, neurocognitive measures have shown limited, albeit consistent, relation to clinical symptoms but appear more closely related to functional outcome. Although the literature evaluating the specificity of deficits in schizophrenia is limited, the profile, and severity seem different from other disorders with psychotic features, such as bipolar disorder. Thus, early evaluation may have diagnostic and treatment implications.



Neuropsychological studies have found impairments in multiple domains, including perception, attention, visuospatial abilities, language, memory, emotion, executive function, and coordination. Within this pattern of diffuse impairment, attention, working and episodic memory, and executive functioning are more severely impaired. Several brain systems are implicated by these deficits. The attention-processing-circuitry includes brainstem-thalamo-striato-accumbens-temporal-hippocampal-prefrontal-parietal regions. Deficits in working memory implicate the dorsolateral prefrontal cortex, and the ventromedial temporal lobe is implicated by deficits in episodic memory. A dorsolateral-medial-orbital-prefrontal cortical circuit mediates executive functions. These are obviously complex systems, and impairment in one may interact with dysfunction in others. Studies with large samples are needed to test models of underlying pathophysiology.

Emotion. In addition to the marked cognitive impairment, emotion-processing deficits have also been noted in schizophrenia, and a growing literature indicates their contribution as neurobehavioral probes. Emotional impairment in schizophrenia is clinically well established, manifesting in flat, blunted, inappropriate affect and depression. Studies have reported emotion-processing deficits in identification, discrimi-

nation, and recognition of facial expressions. Although these deficits may represent a component of the generalized cognitive impairment, they relate to symptoms and neurobiological measures, encouraging further research. Animal and human investigations have implicated the limbic system, primarily the amygdala, hypothalamus, mesocorticolimbic dopaminergic systems, and cortical regions, including orbitofrontal, dorsolateral prefrontal, temporal, and parts of parietal cortex.

Olfaction. Patients with schizophrenia are impaired in their ability to detect and identify odors. Olfactory deficits are present at the onset of illness, do not relate to disease severity or treatment, and are possibly progressive. It is unclear whether the deficits are part of the generalized neurocognitive impairment, but they are evident even when patients perform similarly to healthy participants on tasks designed as control measures. The neuroanatomical differences noted in MRI studies of patients relative to healthy controls suggest that olfactory bulb changes and medial temporal lobe abnormalities could mediate the observed behavioral aberrations.

Linking Deficits to Brain Function. The link between neurobehavioral deficits and brain dysfunction can be examined both by correlating individual differences in performance with measures of brain anatomy and through the application of' neurobehavioral probes in functional imaging studies. With these paradigms, the topography of brain activity in response to engagement in tasks in which deficits have been noted in patients can be investigated. Thus, there is "on-line" correlation between brain activity and performance that permits direct examination of brain behavior relations.

NEUROANATOMICAL STUDIES IN SCHIZOPHRENIA

Neuroanatomical correlates of impaired performance have provided the foundation for current thinking about brain regulation of behavior. As noted in the previous section, the

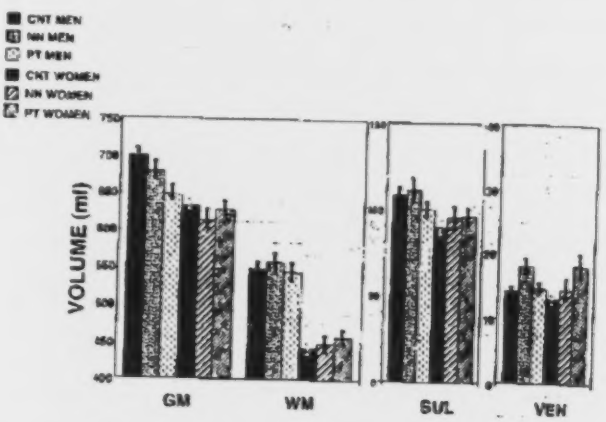
behavioral aberrations manifested in schizophrenia implicate. diffuse abnormalities likely to involve several brain systems. Defining the neuroanatomical differences and possible changes associated with schizophrenia is, arguably, a prerequisite for understanding its neural substrates and interpreting functional studies of brain physiology and neurochemistry. Structural morphometric studies have applied reliable computerized segmentation methods for obtaining volumetric measures. The improvement in precision of neuroanatomical parameters has yielded some consistency in effects and correlations with clinical and neurobehavioral measures. This section briefly highlights and illustrates these research efforts, starting with whole-brain effects, and then describes some regional effects.

Brain and Cerebral Spinal Fluid Segmentation Multiple studies with MRI examining whole-brain and cerebrospinal fluid (CSF) volumes have indicated smaller brain volume and increased CSF in patients with schizophrenia relative to healthy people The increase is more pronounced in ventricular than sulcal CSF. There is, however, considerable overlap between patients and healthy people, suggesting that abnormalities at the level of whole brain may characterize only subtypes of patients with schizophrenia. Brain and CSF volumes have been related to phenomenological and other clinical variables, such as premorbid functioning, symptom severity, and outcome. Abnormalities in these measures are likely to be more pronounced in patients with poorer premorbid functioning, more severe symptoms, and worse outcome. The concept of brain reserve that has been suggested in other disorders, such as Alzheimer's disease, may apply to schizophrenia as well. Thus, normal brain and CSF volumes are preliminary indicators of protective capacity. As understanding of how brain systems regulate behavior in health and disease has improved, it has become possible to take advantage of neuroimaging to examine specific brain regions implicated in the pathophysiology of schizophrenia.

Gray Matter and White Matter Segmentation. Gray matter and white matter tissue segmentation, particularly feasible with thin-sliced, TI-weighted MRI sequences provides anatomical information supplementing the demarcation of brain and CSF. Gray matter changes have been found during adolescence and in the course of the normal aging process. Gray-white segmentation is critical in developmental studies in which age-related decreases in gray matter may be obscured by simultaneous increases in total brain and cranial volumes. This image-processing methodology can help determine whether tissue loss and disorganization in schizophrenia are primarily gray matter deficits or whether abnormalities in white matter are also involved. Several studies using segmentation methods have indicated that gray matter volume reduction characterizes individuals with schizophrenia. This reduction is apparent in neuroleptic-naive, first-episode patients and supports the growing body of work indicating that schizophrenia is a neurodevelopmental disorder (Fig. 12.6-2).

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FIGURE 12.6–2 Whole-brain volumes for parenchyma (gray matter [GM] and white matter [WM]) and cerebrospinal fluid (CSF) compartments (sulci [SUL] and ventricle [VEN]) in healthy men and women (control [CNT]) and in people with schizophrenia (neuroleptic-naive [NN] and previously treated [PT]). (Adapted from Gur RE, Turetsky BI, Bilker WB, Gur RC: Reduced gray matter volume in schizophrenia. Arch Gen Psychiatry 1999;56:905.)



Regional Volumes. In evaluating specific regions, the most consistent findings are of reduced volumes of temporal lobe, superior temporal gyrus, and medial temporal lobe structures. Other brain regions have also been noted to have reduced volumes, although less consistently. These include the prefrontal cortex, parietal lobe, thalamus, basal ganglia, cerebel-

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lar vermis, and olfactory bulbs. The application of diverse methods may partly explain discrepant results. For example, morphometric prefrontal studies differed in magnetic field, scanning parameters, slice thickness and contiguity, image processing, and regions examined. Consequently, findings seem inconsistent, with some noting no differences between patients and healthy participants, and others observing volume reduction in gray matter, white matter, or both tissue compartments.

Relatively few studies have related sublobar volumes to clinical or neurocognitive measures. Higher right orbitofrontal volume was associated with positive symptom severity in men with schizophrenia in one study, and dorsolateral volume was related to performance on abstraction, attention, and memory in another study. Despite sample sizes and partial inclusion of subfrontal regions, these studies support the hypothesis that increased volume is associated with better performance. In a sample of 70 patients and 81 healthy participants, reduced gray matter volume was observed in the dorsolateral prefrontal cortex (Fig. 12.6-3). The effects were moderated by sex for dorsomedial and orbital regions: In men with schizophrenia, reduced volume was specific to the dorsolateral prefrontal sector, whereas in women, it was reduced in both the orbital and dorsal regions. Greater volume reductions were associated with higher symptom severity and poorer cognitive function.

For the temporal lobe, global lower volume was reported, as well as reduced gray matter but not reduced white matter, with lateralization to the left hemisphere. Regional analysis indicated decreased volume in temporolimbic structures, including the hippocampus (Fig. 12.6-4), parahippocampal gyrus, and amygdala. However, the results are not consistent, and some studies did not report differences in these regions. A metaanalysis examined 18 studies measuring hippocampal volumes, sometimes combined with amygdala. Bilateral hip-

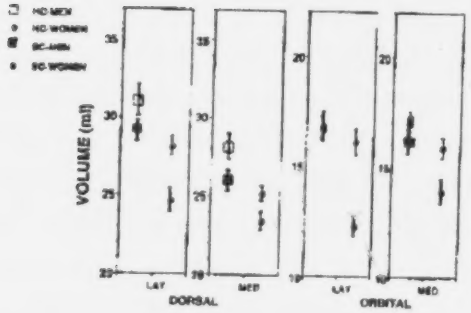


FIGURE 12.6–4 Volume of frontal subregions in healthy controls (HC) and in patients with schizophrenia (SC). LAT, lateral; MED, medial. (From Gur RE, Cowell PE, Turetsky BI, et al. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Arch Gen Psychiatry* 2000;57:761, with permission.)

pocampal reduction had a significant effect size, and adding amygdala further increased it. Laterality effects were inconclusive. Cortical temporal regions, especially the superior temporal gyms, have also been evaluated. Reduced volume has been observed in anterior, posterior, and total superior temporal gyrus and was related to severity of auditory hallucinations and thought disorder. However, other studies have not noted a decrease in superior temporal gyrus volume.

More recently, efforts have focused on identifying neuroanatomical substrates that may relate to clinical subtypes. For example, patients were divided by whether their memory suggested cortical or subcortical dementia. Patients with cortical deficits were more likely male with an earlier age at disease onset and had reduced temporal lobe gray matter. Patients who had memory deficits characteristic of subcortical dementia had ventricular enlargement and more negative symptoms.

Longitudinal Studies. Of note is that the observed volume reductions in schizophrenia are evident at first presentation before treatment, The question of progression of parenchymal tissue loss has been addressed in relatively few studies. Longitudinal studies applying MRI have examined first-episode patients. This is an informative population because the design enables prospective follow-up starting early in the

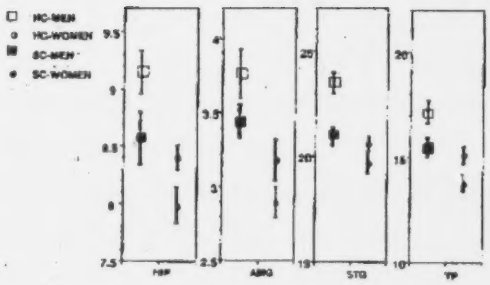


FIGURE 12.6–4 Volume of temporal subregions in healthy controls (HC) and in patients with schizophrenia (SC): controls minus patients. AMG, amygdala; HIP, hippocampus; STG, superior temporal gyrus; TP, temporal pole. (From Gur RE, Turetsky BI, Cowell PE, et al.: Temporolimbic volume reductions in schizophrenia. *Arch Gen Psychiatry* 2000;57:769, with permission.)

course of illness. One group of investigators found no ventricular changes in a follow-up of 13 patients and 8 controls conducted 1 to 2 years after the initial study. Another study evaluated 16 patients and five controls 2 years after a first psychotic episode. Patients showed no consistent change in ventricular size with time, although there were individual increases or decreases. With a slightly larger group of 24 patients and six controls, no significant changes were observed in ventricular or temporal lobe volume at follow-up. Subsequently, 20 of these patients and five controls were rescanned over 4 years, and greater decreases in whole-brain volume and enlargement in left ventricular volume were observed in patients. The authors of the study concluded that subtle cortical changes may occur after the onset of illness, suggesting progression in some cases,

In a longitudinal study. 40 patients (20 first-episode, 20 previously treated) and 17 healthy participants were rescanned an average of 2.5 years later. The volumes of whole brain CSF, and frontal and temporal lobes were measured. The severity of negative and positive symptoms was assessed, medications were monitored, and neurobehavioral functioning was evaluated. First-episode and previously treated patients had smaller whole-brain, frontal, and temporal lobe volumes than controls at intake. Longitudinally, reduction in frontal lobe volume was found only in patients, whereas temporal lobe reduction was also seen in controls. The associa-

tion between volume reduction and symptom change differed between patient groups, but in both first-episode and previously treated patients, volume reduction was associated with decline in some neurobehavioral functions.

The question of specificity of neuroanatomical findings to schizophrenia was addressed in a recent study that evaluated 13 patients with first-episode schizophrenia, 15 patients with first-episode affective psychosis (mainly manic), and 14 healthy comparison subjects longitudinally with scans separated by 1.5 years. The investigators reported that patients with schizophrenia had progressive decreases in gray matter volume over time in the left superior temporal gyrus compared with both other groups. The existence of neuroanatomical abnormalities in first-episode patients indicates that brain dysfunction occurred before clinical presentation. However, the longitudinal studies suggest evidence of progression in which anatomical changes may impact some clinical and neurobehavioral features of the illness in some patients.

MRI findings have been most consistent for gray matter volume reduction. More recently, white matter changes have also been reported. The availability of diffusion tensor imaging will enhance the efforts to examine compartmental abnormalities. The growing understanding of brain development and MRI data obtained from children suggests that the neuroanatomical neuroimaging literature in schizophrenia is consistent with diffuse disruption of normal maturation. Thus, there is clear evidence for structural abnormalities in schizophrenia associated with reduced cognitive capacity and less clear evidence for structural abnormalities with symptoms. Future work, perhaps with more advanced computerized parcellation methods, is needed to better chart the brain pathways that are most severely affected.

FUNCTIONAL IMAGING STUDIES OF SCHIZOPHRENIA

Functional imaging methods examine brain activity through measures related to energy metabolism, such as rates of glucose and oxygen use and CBF. Methods include PET for glucose metabolism and CBF, SPECT for CBF, and fMRI for measuring changes in signal intensity attributable to CBF. Neuroreceptor function can be assessed using methods for measuring receptor density and affinity at presynaptic and postsynaptic sites. Both PET and SPECT studies have been conducted in people with schizophrenia.

CEREBRAL METABOLISM AND BLOOD FLOW STUDIES

Studies of regional cerebral metabolism and blood flow can be globally divided into those measuring the physiological parameters at a resting state and those introducing a perturbation, or challenge, in the form of a neurobehavioral probe or a pharmacological intervention initially, investigators have tried to assess whether resting CBF and glucose metabolism differ between patients with schizophrenia and healthy controls. The topography of physiological activity was examined along dimensions that may provide useful information regarding brain organization and function: anterior-posterior, subcortical-cortical, and laterality.

Resting Baseline. The frontal lobes were implicated in early physiological studies of CBF that reported that patients did not show the normal pattern of increased anterior CBF relative to posterior CBF. This hypofrontal disturbance in the anterior-posterior gradient has been supported by some, but not all, studies of resting CBF with the xenon-133 (^{133}Xe) and SPECT and glucose metabolism with PET. The relationship between this pattern of metabolic activity and clinical variables has also been examined. Duration of illness and negative symptoms were associated with decreased frontal meta-

bolic activity. Longer course of illness and more severe negative symptoms were associated with lower anteroposterior gradient.

Differences in resting values between patients and controls were also found in laterality indices, suggesting relatively higher left hemispheric values in more severely ill patients. Furthermore, improvement in clinical status correlated with a shift toward lower left hemispheric metabolism relative to right hemispheric metabolism. This supports hypotheses derived from behavioral data concerning lateralized abnormalities in schizophrenia.

After assessing global, anterior-posterior, and laterality dimensions, investigators have begun the study of functional changes in brain systems linked to other impaired behavior in schizophrenia. Dysfunction in temporal limbic structures, including the hippocampus and temporal cortex is supported by neuroanatomical and neuropsychological studies. Lateralized abnormalities in these regions, with greater left than right hemispheric dysfunction, are implicated by characteristic clinical features of schizophrenia, such as thought disorder, auditory hallucinations, and language disturbances. PET studies of temporal lobe metabolism include findings of both increased and decreased glucose use. Decreased metabolism was also noted in the hippocampus and anterior cingulate cortex.

Metabolism and flow pattern in temporolimbic regions have also been related to symptoms. An oxygen-15 (^{15}O)—labeled water study with PET described abnormal CBF in parahippocampal gyrus associated with positive symptoms. Hallucinations were associated with SPECT flow changes in the hippocampus, parahippocampus, and amygdala. There are conflicting reports of superior temporal gyms functional changes in schizophrenia during active auditory hallucinations. Although one study suggested that patients with hallucinations have significantly lower relative metabolism in

Wernicke's region, another study showed asymmetrical temporal lobe perfusion, lower in the left than the right, in patients with auditory hallucinations. In one PET study, the rate of glucose metabolism was greater in the left anterior temporal lobe, which was related to the severity of symptoms. This is consistent with another reported association between severity of symptoms and relative increase in left hemispheric metabolism.

These reports varied in the technology applied and definition of regional parameters. Most studies used ratios, such as region to whole brain or anterior to posterior, rather than absolute values of activity. Inconsistencies in findings could also be related to sample size, heterogeneity, analytical approaches, and individual techniques. Most studies included relatively small samples of patients that varied in important clinical factors, such as chronicity, symptom subtypes and severity, level of functioning, and history of treatment. Furthermore, inclusion criteria varied, and some laboratories applied more stringent criteria related, for example, to history of comorbidity of substance abuse and head trauma with loss of consciousness. Another potential source of variability in results is the definition of resting state. Some studies used reduced sensory input, and others used sensory stimulation to standardize this condition. However, several studies have examined the reproducibility of resting baseline measures with relatively unstructured conditions (i.e., eyes open and ears unoccluded, with ambient noise kept to a minimum). These studies found very high reproducibility among healthy subjects and patients with schizophrenia.

Given the demonstrated reliability of the standardized resting baseline condition, it is important to include such a condition in physiological neuroimaging studies. A standardized resting baseline serves three main purposes. First, it permits comparison across studies within a center as technology evolves and patient characteristics change. Without a com-

mon resting baseline condition it would be impossible to determine the source of differences in results. Second, it enables comparability across centers. Imagine the need to explain why two centers using the same or similar tasks find evidence for different regional abnormalities in schizophrenia. If resting baseline values are available and are comparable in the two samples, different task effects could be legitimately attributed to theoretically meaningful sources, such as task condition or symptomatic variability. Third, it provides a reference point for evaluating whether a given task or condition has increased neural activity. In studies that have included such a condition-cognitive activation was consistently shown to increase, cortical activity in both patients and controls relative to a resting baseline. Using a resting baseline condition enables the investigator to make much stronger statements in the interpretation of regional effects. Rather than being restricted to statements that a given region has changed in its activation relative to the remainder of the brain, resting baseline availability permits stating whether the task has induced increased neural activity.

Functional changes in the basal ganglia have been examined with PET and SPECT. Several PET studies implicate basal ganglia dysfunction in schizophrenia. The withdrawal-retardation factor (emotional withdrawal, blunted affect. and motor retardation) of the Brief Psychiatric Rating Scale (BPRS) has been negatively correlated with PET basal ganglia metabolic activity. Neuroleptic-naive patients were reported to have relatively increased blood flow in the left globus pallidus. Other PET studies report decreased basal ganglia metabolism in schizophrenia, whereas still others found increased basal ganglia metabolic rates after administration of neuroleptic medication.

Thus, although the contribution of PET metabolic and blood flow studies so far has been to add to the growing evidence implicating basal ganglia involvement in schizo-

phrenia, the exact nature of the dysfunction remains unclear. In particular, the relationship between basal, ganglia, and frontal lobe activity in schizophrenia needs further scrutiny. There is emerging evidence, revealed by structural and functional imaging, of a dynamic interrelationship between the various key regions. One study showed that patients with schizophrenia not only fail to activate dorsolateral prefrontal cortex in response to the Wisconsin Card Sorting Test, but they also fail to inhibit caudate activation. Hence, in patients with schizophrenia, basal ganglia continue to show relatively increased flow in caudate during performance of the task, as opposed to healthy controls, who seem to demonstrate a reciprocal relationship in which relative blood flow decrease in the basal ganglia is associated with increasing perfusion to the frontal region.

Activation Studies. Measures of CBF and metabolism during the performance of cognitive tasks tend to accentuate differences between patients and controls. Perhaps even more important, such measures are critical for establishing the link between behavioral deficits and the ability of brain regions to become activated in response to task demands. This expectation has been supported in studies that used neurobehavioral probes.

The general approach in the field has been to work from hypotheses derived from neurobehavioral data which associate behavioral measures with regional brain function. Task selection can be made to include a target task, in which patients are expected to have differential deficit, and control tasks. Patients are then compared to healthy participants in the pattern of task-induced changes in regional brain activity. This has now become the established research paradigm and significant progress has been made in elucidation of brain systems underlying healthy and pathological behavior.

Early studies obtained CBF resting and performance measures. Although no differences were noted in overall or hemi-

spheric CBF between patients and controls at resting baseline, distinct abnormalities were seen when physiological activity was measured in response to cognitive probes. The nature of the dysfunction was related to the hypothesis examined. For example, pursuing the laterality hypothesis, tasks were administered with demonstrated links to left (verbal) and right (spatial) hemispheric functioning. Healthy controls showed the expected greater left hemispheric increase for the verbal task and greater right hemispheric increase for the spatial task. However, patients with schizophrenia had a bilaterally symmetrical activation for the verbal task and greater left hemispheric activation for the spatial task. Thus, patients did not show the normal left hemispheric dominance for the verbal task and, instead, showed left hemispheric overactivation for the spatial task. Similarly, distinct abnormalities were reported in the dorsolateral prefrontal region during activation with the Wisconsin Card Sorting Test of abstraction and mental flexibility, which is sensitive to frontal lobe damage. The application of this paradigm to the study of monozygotic twins discordant for schizophrenia revealed that all affected twins had reduced dorsolatera] prefrontal cortex CBF response compared to discordant co-twins. Furthermore, negative symptoms, which have been related to frontal lobe dysfunction, showed a negative correlation with frontal CBF during performance of executive but not control tasks.

Probing brain systems with specific tasks has also been advanced in SPECT and in CBF studies with PET. These methods have also indicated abnormalities in patients with schizophrenia-with a range of tasks, including memory and executive and attentional measures (Fig. 12.6-5).

In a PET study of cerebral blood now with oxygen-15-labeled water, research participants performed word encoding and word retrieval tasks. While patients with schizophrenia has similar performance to healthy controls, they had reduced cerebral activity in left frontotemporal areas during episodic

encoding. These regions were activated during subsequent retrieval, but reduced activation during encoding correlated with poorer recognition performance. This may reflect impaired strategic use of semantic information to organize encoding and facilitate retrieval in schizophrenia. Applying the same PET methodology, another study examined the effects of encoding interventions, such as item repetition and the formation of semantic associations, on hippocampal activity. Healthy controls recalled more words, but both groups improved performance after encoding intervention. However, the pattern of brain activity differed. In healthy controls, but not in participants with schizophrenia, increased hippocampal blood flow was observed. In patients, greater activation of prefrontal regions was noted during word retrieval.

The consistent finding emerging is lack of normal regional activation in response to task and activation in some regions not seen in healthy subjects. These results suggest that brain systems recruited for the performance of specific tasks in healthy people are not engaged in a similar manner in patients with schizophrenia. What might account for such aberrations? Genetic liability, neurodevelopmental abnormalities in which brain systems fail to achieve maturity, or the impact of a psychotic process that interrupts normally developed structures and processes? Does therapeutic intervention ameliorate the abnormal signature? How specific are the results to schizophrenia? These are some of the questions yet to he answered that can be addressed with neuroimaging.

Functional MR. The introduction of fMRI is an exciting, more recent development in functional imaging research. fMRI methods offer several potential advantages over PET for imaging brain function, including higher spatial resolution, higher temporal resolution, noninvasiveness and lack of ionizing radiation, direct correlation with anatomical imaging, greater repeatability, and economy. Disadvantages of fMRI techniques include the presence of loud background noise

generated by the gradient shifts, difficulties in presenting stimuli and performing tasks in the magnet bore, claustrophobia, low signal-to-noise ratio for most methods, and lack of quantitation in physiological units for most methods. Many of these disadvantages can be overcome through the use of specialized equipment compatible with the MRI environment. These methods will be described briefly, because they are recent and hold potential for functional imaging in schizophrenia.

The blood oxygen level dependent (BOLD) method has been most widely applied to fMRI, with results replicating previous PET studies. The technique relies on magnetic susceptibility effects of deoxyhemoglobin, which cause regional decreases in signal in imaging sequences that are sensitive to susceptibility (e.g., echoplanar or routine gradient echo sequences). With regional brain activation studies, a net increase in signal intensity is observed in regions known to be activated by the task. The increase in image intensity corresponds to a local decrease in deoxyhemoglobin. This finding is attributed to a greater increase in regional blood flow than in regional oxygen consumption, a notion supported by PET measurements of blood flow and oxygen consumption with regional brain activation. A wide variety of pulse sequences can be used to obtain BOLD measures. Many simple activation paradigms have been tested, and activation has been observed with both fast and slow imaging. A typical response is a 1 to 25 percent change in regional image intensity that develops over 3 to 8 seconds after task initiation. Susceptibility effects of deoxyhemoglobin are field dependent. Thus, a scanner with 1.5-tesla field strength would typically record signal changes with functional activation of approximately 0.25 to 5.0 per-cent, whereas, at 4 tesla, changes up to 25 percent have been observed. The main advantages of ultrafast imaging are that time course of signal change can be observed and multislice imaging can be carried out in a reasonable period.

Arterial spin tagging (quantitative perfusion imaging) uses magnetization tagging of endogenous arterial water to determine perfusion of brain parenchyma by comparing images obtained with and without labeling of the arterial supply. The method is analogous to steady-state techniques used in PET, as the regional signal intensity is dependent on the arterial blood flow that delivers labeled spins and the TI relaxation rate, which causes the labeling to decay. This technique has the important advantage of providing quantitative CBF parameters. Furthermore, perfusion is measured in brain parenchyma directly and is, thus better localized than measurements obtained using an intravascular tracer, which is most sensitive to venous outflow effects. There may also be less motion sensitivity than with BOLD.

The transition from isotopic methods to fMRI for measuring regional brain activation has been embraced by investigators, because of the advantages offered. Consequently, numerous experiments have applied neurocognitive paradigms in fMRI studies aimed at dissecting complex behavior. Most of these studies have involved healthy people, applying the BOLD method using blocked designs and, more recently, event-related paradigms. Relative to the wide range of neurocognitive processes examined in healthy people, there have been fewer fMRI studies in schizophrenia. Studies have reported abnormal activity in response to motor tasks, working memory, attention, word fluency, emotion processing, and medication effects in 15-tesla scanners. More recent investigations have been conducted in higher fields. These functional neuroimaging studies-have successfully linked deficits in performance to abnormalities in activation patterns.

In one study of word memory, patients had reduced activation in anterior prefrontal, posterior cingulate, and retrosplenial areas during word encoding. The word recognition task was associated with reduced activation in the patients' dorsolateral prefrontal and limbic/paralimbic regions: Yet,

higher activity was observed in bilateral anterior prefrontal cortices. Thus, it appears that patients do not recruit the same neural circuitry as healthy people.

Given the documented deficits in emotion processing associated with schizophrenia, fMRI studies have targeted emotion circuitry with neurobehavioral probes using predominately facial stimuli. Overall, studies have reported reduced limbic activation in schizophrenia both for mood induction effects and for emotion discrimination tasks. For example, in one study, participants viewed facial displays of happiness, sadness, anger, fear, and disgust, and neutral faces. Their task alternated between emotion and age discrimination with a cross-hair reference condition interleaved. Patients and healthy controls did not differ in performance on either task. However, there were voxels in the left amygdala and bilateral hippocampus in which controls had significantly greater activation than patients. Failure to activate limbic regions during emotional valence discrimination may explain emotion-processing deficits in patients with schizophrenia. Although the lack of limbic recruitment did not significantly impair simple valence discrimination performance in this clinically stable group, it may impact performance of more demanding tasks (Fig. 12.6-6).

Methodological Considerations and Treatment Effects. Task difficulty and effort must be investigated to understand the mechanisms through which disturbed behavior emanates from abnormal activation. Differences in activation patterns can be difficult to interpret in the face of differences in performance. The underlying assumption in the measurement of brain activation is that neuronal activity drives mental effort. Given comparable basal abilities, greater activation should relate to better performance. However, in schizophrenia, it is unclear how a finding of reduced or increased activation should be interpreted. One approach is to make the tasks easy so that patients and controls perform equally. However, the

truncated performance range in the healthy group limits the ability to associate performance to brain activation. More difficult tasks in which individual differences can be examined are necessary to better understand abnormal brain circuitry.

A host of clinical variables requires attention in functional imaging studies. These variables include patient subtype, severity of symptoms, and treatment status. The complexity of the studies and their typically small samples result in limited conclusions. Considering treatment, the pharmacological status of patients undergoing metabolic and blood flow studies has varied. Research has ranged from investigations in which neuroleptics were considered a variable to be controlled to those in which pharmacological intervention was introduced in a standardized fashion to examine treatment effects on the regional metabolic landscape. The washout period in studies that attempted to control the effects of neuroleptics on CBF and metabolism has typically been short, ranging from 2 to 4 weeks. This period is a compromise between what is feasible and what is desirable. A large sample of unmedicated men with schizophrenia underwent a PET cerebral glucose metabolism study, and cortical-striatal-thalamic circuitry was evaluated. Low metabolic activity in medial frontal cortical regions and the basal ganglia, as well as an impaired lateralization pattern in frontal and temporal regions, was observed in the patient group. The inclusion of neuroleptic-naive, first-episode patients is particularly informative when the focus of the study is the effects of pharmacological intervention. The study of neuroleptic-naive patients before pharmacological intervention permits evaluation of the disease state separate from its treatment. The pattern of abnormalities is evident in first-episode patients across studies that examined differences between their first episode and episodes of previously treated patients. This suggests that disruption in normal brain processes is already apparent at the presentation of illness and cannot he attributed to treatment or chronicity.

A repeated-measures longitudinal design has been applied in a limited number of functional imaging studies. In addition to examining the symptom severity over time, this paradigm is particularly useful when pharmacological intervention is standardized. One study compared the effects of thiothixene (Navane) and haloperidol (Haldol) in chronic patients who were scanned off medication and after 4 to 6 weeks on medication. A different pattern of global and regional glucose metabolism was seen in the two groups. In another study, PET scans were obtained at weeks 5 and 10 of a double-blind, crossover trial of haloperidol and placebo in 25 patients with schizophrenia. Low relative metabolism in the striatum on placebo was associated with improved symptomatology. Responders to treatment had increased metabolism in the striatum after treatment. Nonresponders failed to show such a change and had more marked hypofrontality on medication. In a subsequent study, 12 patients were scanned before and 4 to 6 weeks after treatment with clozapine (Clozaril) or thiothixene. The drugs had a differential effect, with clozapine increasing metabolism and thiothixene decreasing metabolism in the basal ganglia (right more than left). Henry Holcomb and colleagues, in a repeated-measures design studied glucose metabolism in 12 patients when on a fixed dose of haloperidol and 5 and 30 days after drug withdrawal. No differences were observed between metabolism on medication and after 5 days of discontinuation. However, at 30 days, decreased metabolism was noted in the caudate, putamen, and anterior thalamus, whereas there was an increase in the frontal cortex and anterior cingulate. The authors of the study concluded that the basal ganglia is the site of primary antidopaminergic action of haloperidol and that other changes observed are mediated through the striatal-thalamic-cortical pathways. The integration of pharmacological and neurobehavioral probes is a potentially powerful approach. For example, it was noted that in patients with schizophrenia there was enhanced activa

tion of the anterior cingulate after administration of apomorphine suggesting a modulating role for dopamine.

Application of neurobehavioral probes during functional imaging studies is a productive avenue in the effort to define involvement of neural systems in the pathophysiology of schizophrenia. Such neurobehavioral probes document deficits in performance associated with abnormal brain activation, perhaps sparing the sensory domain and implicating the ventromedial temporal lobe, prefrontal cortices, and limbic subcortical nuclei, which mediate memory, executive functioning, and attention. These systems are characterized by dynamic plasticity, high connectivity, and vulnerability to insult, consistent with the hypothesis that abnormal plasticity is a core neurobiological feature of schizophrenia. Such fundamental mechanisms of abnormal structural, molecular, or physiological plasticity should be evident throughout the central nervous system (CNS) but most prominently expressed in neural systems mediating activity-dependent cognitive processes of attention, memory, and executive functioning.

NEURORECEPTOR STUDIES

Study of Neuroreceptors. The study of neuroreceptors is another critical window for assessing brain function and can give insight on the nature of neurochemical abnormalities in schizophrenia. Because advances in elucidating the pathophysiology of schizophrenia require understanding of neurotransmitter function, the application of PET and SPECT to the study of receptors is an important domain with treatment implications. These efforts are guided both by an extensive psychopharmacological literature, and by advances in basic neuroscience on neuroreceptor subtyping. Functional neuroimaging is the meeting ground of preclinical and clinical neuropharmacology. Human neuroreceptor PET studies have built on progress with in vitro binding measurements of receptor density and affinity and neuroreceptor autoradiography.

PET and SPEC Studies. Earlier work with radioligands for PET studies focused on the dopamine type 2 (D_2) receptor. The psychotic symptoms noted in schizophrenia have been associated with dysfunction of dopamine, which is targeted in treatment with neuroleptics. Two major methodologies for quantitative measurement were developed and applied in the study of schizophrenia. One set of studies applied [^{11}C] *N*-methylspiperone and reported that patients relative to controls have higher D_2 maximal binding capacity (B_{max}) values. A second set of studies using [^{11}C]raelopride reported similar B_{max} and distribution coefficient (K_d) values in patients and controls. These apparent differences have been discussed and summarized extensively and are likely related to multiple factors, including patient variables, ligand properties, and PET modeling methods. Because the ligands differ in binding properties and sensitivity to endogenous dopamine, studies permitting a more direct comparison have been instructive. For example, the reproducibility of the [^{11}C] *N*-methylspiperone finding in a study of seven neurolepticnaive patients and seven controls before and after administration of 7.5 mg of haloperidol was examined. Consistent with a previous quantitative PET study of [^{11}C]raclopride binding, there were no differences between patients and controls pretreatment, and, after haloperidol, the specific binding of [^{11}C] *N*-methylspiperone was reduced by 80 to 90 percent. In further efforts, the initial results obtained with [^{11}C] *N*-methylspiperone were replicated in a new sample of drug-naive patients with schizophrenia. Other data revealed that D_2 density increased in psychotic patients but not in nonpsychotic patients with bipolar disorder. The degree of increase was comparable to that reported in schizophrenia. This raises questions regarding the specificity of the dopamine hypothesis to schizophrenia versus other disorders with psychotic features.

Other ligands have also been applied. For example, D_2 striatal dopamine receptors were evaluated with [^{76}Br] bromospiperone in PET studies of untreated patients with schizo-

phrenia compared to healthy people. There was no increase in striatum to cerebellum ratios of D_2 receptors in patients relative to controls, and no relation to symptoms or subtypes emerged. A PET study with ^{11}C-FLB 457, a radioligand for extrastriatal D_2 dopamine receptors, examined 11 drug-naive men with schizophrenia and 18 healthy controls. Extrastriatal binding potential differences were observed in the anterior cingulate cortex, where patients had a 12.5 percent reduction relative to controls.

The D_2 receptor SPECT ligand iodide-benzamide [^{123}I] iodobenzamide (IBZMl) has been applied in studying dopamine D_2, receptors in patients with schizophrenia. In earlier work, a large sample of 56 patients was evaluated and a semiquantitative analysis of D_2 receptor binding was calculated (basal ganglia to frontal cortex ratio of activity). The basal ganglia to frontal cortex ratios in patients taking typical neuroleptics were significantly lower than those of the neuroleptic-free patients but not lower than those of patients taking the atypical agents clozapine and remoxipride. No overall elevation of D_2 receptor binding was observed when comparing 20 patients off medications and 20 controls, a finding similar to PET studies that examined D_2 receptor occupancy.

D_1 dopamine receptor function in schizophrenia was also examined in PET studies. ^{11}C-labeled SCH23390 with high and low specific radioactivity was administered to ten neuroleptic-naive patients and ten controls. There were no differences between the two groups in receptor density and affinity measured in the caudate nucleus, the putamen, and several neocortical regions. Other ligands are currently being applied to evaluate serotonergic and muscarinic function with both PET and SPECT ligands.

Receptor Function and Clinical Response. The study of neuroreceptors can also address issues related to the relationship between receptor function and clinical signs, such as akathisia, commonly seen in patients treated with conven-

tional neuroleptics. Thus, for example, PET studies at low and high doses of [^{11}C]SCH23390, a selective D_1 dopamine receptor antagonist, were conducted in healthy people. Transient akathisia occurred only when binding in the basal ganglia was at a high level, with 45 to 59 percent occupancy. The D_2 dopamine receptor antagonist [^{11}C]raclopride was measured in 13 patients with schizophrenia and 20 healthy participants. Akathisia was associated in patients and controls with maximal ligand binding in the basal ganglia. Other clinical features have been evaluated in relation to receptor function. Treatment resistant patients did not differ from neuroleptic responders in degree of D_2 receptor occupancy by the neuroleptic agents. The regional distribution and kinetics of haloperidol binding were studied with [^{18}F]haloperidol in a PET study of five patients with schizophrenia examined while on haloperidol and after a drug washout and nine controls. Wide regional distribution of the ligand was evident in the cerebellum, basal ganglia, and thalamus, in contrast to the specific binding to the basal ganglia of [^{18}F] *N*-methyispiroperidol. Thus, small structural differences among butyrophenones are associated with changes in kinetics and distribution.

Typical and Atypical Antipsychotics. PET neuroreceptor methods have also been applied in the study of atypical antipsychotic drugs compared to typical antipsychotic drugs. The properties of clozapine binding to D_1 and D_2 dopamine receptors were examined in an open study of 5 patients relative to 22 patients treated with typical neuroleptics. Clozapine induced lower D_2 occupancy (38 to 63 percent), whereas D_2 receptor occupancy with typical neuroleptics at conventional doses was 70 to 89 percent. Neuroleptic-induced extrapyramidal syndromes were associated with higher D_2 occupancy. In a follow-up study, the relationship between D_2 receptor occupancy and antipsychotic drug effect was examined in a double-blind study using [^{11}C]raclopride. Seventeen patients with schizophrenia were randomly assigned to three groups treated with a varied dose of raclopride. A PET study was

conducted at steady state on 13 patients during the third to fourth week of treatment. A curvilinear relationship between plasma concentration of raclopride and D_2 receptor occupancy was obtained. A significant relationship was noted between D_2 receptor occupancy and Brief Psychiatric Rating Scale percent change as a measure of outcome. The D_2 receptor occupancy in patients who had extrapyramidal side effects was higher than in patients with no extrapyramidal side effects. Further work examined D_1, D_2, and 5-hydroxytryptamine type 2 (5-HT_2) receptor occupancy in 17 patients treated with clozapine (125 to 600 mg per day) applying [^{11}C]SCH23390. ^{11}C-raclopride, and [^{11}C] *N*-methylspiperone. D_2 receptor occupancy (20 to 67 percent) was lower than for typical neuroleptics (70 to 90 percent), D_1 receptor occupancy (36 to 59 percent) was higher than that reported for typical neuroleptics (0 to 44 percent), and 5-HT_2 receptor occupancy was high (84 to 94 percent). Thus, clozapine shows a combination of relatively high D_1, low D_2, and very high 5-HT_2 receptor occupancy values, with serum concentrations not predictive of degree of receptor occupancy. In a PET study of [^{11}C]raclopride, another group of investigators determined D_2 receptor occupancy induced by 2 mg per day of haloperidol for 2 weeks in seven patients. High levels of D_2 occupancy (53 to 74 percent) were noted with substantial clinical improvement. A similar investigation in nine patients receiving 2 to 6 mg per day of risperidone (Risperdal) showed receptor occupancy (66 to 79 percent) similar to that of typical neuroleptics and higher than that of clozapine.

Another study that illustrates the implications of this line of research to treatment evaluated seven first-episode or drug-free patients. They were treated with risperidone, 6 mg per day for 4 weeks, and then 3 mg per day for 2 weeks. PET studies were performed after 4 and 6 weeks, with [^{11}C]raclopride to measure D_2 receptor occupancy and [^{11}C] *N*-methylspiperone to measure 5-HT_{2A} receptor occupancy.

Participants were treatment responsive, and none had extrapyramidal side effects when entering the study. At the 6-mg-per-day dose, mean D_2 receptor occupancy was 82 percent (range, 79 to 85 percent), 5-HT_{2A} receptor occupancy was 95 percent (range, 86 to 109 percent), and 6 patients had developed extrapyramidal side effects. After dose reduction to 3 mg per day, D_2 receptor occupancy ranged from 53 to 78 percent, and 5-HT_{2A} receptor occupancy range was 65 to 112 percent. Three patients still had extrapyramidal side effects at the reduced dose. This suggests that treatment with 4 mg per day of risperidone can achieve a beneficial antipsychotic effect with a minimal risk of extrapyramidal side effects. A recent study examined the relationship between D_2 receptor occupancy level and subjective experience in patients with recent-onset schizophrenia. Patients were randomly assigned to 6 weeks of double-blind treatment with either olanzapine, 7.5 mg per day, or haloperidol, 2.5 mg per day. Receptor occupancy was assessed with IBZM SPECT. Receptor occupancy between 60 and 70 percent was associated with optimal subjective experience, but variability was evident. This indicates the need for individual titration of dose to reach optimal occupancy.

These research paradigms illustrate the integration of functional neuroimaging with pharmacological research. Incorporation of these strategies into psychopharmacological studies of schizophrenia with available and new therapeutic agents can advance the field and guide treatment intervention.

METABOLITE STUDIES: MR SPECTROSCOPY

MRS provides analytical qualitative and quantitative data on cellular metabolism and molecular structure. It has been used to study metabolism in vitro and in vivo in animals and humans. Spectral localization methods permit the measurement of hydrogen-1 (^1H) and phosphorus-31 (^{31}P) nuclear magnetic resonance (NMR) spectra from precisely localized volumes of interest, and this provides the basis for applying

these techniques to study brain diseases. Because the technology is fundamentally similar to that used in MRI, several groups have developed approaches that integrate these two modalities into a single examination.

There is a growing literature using this method to investigate the underlying metabolism of neuropsychiatric disorders, including schizophrenia. Early work in the field applied ^{31}P methods to the study of schizophrenia, reporting hypofunction in the dorsolateral prefrontal cortex in neuroleptic-naive patients. In the patients, the levels of inorganic phosphate were decreased and the levels of adenosine triphosphate (ATP) were increased. These latter results were interpreted as reflecting hypofunction of the dorsal prefrontal cortex. This interpretation is consistent with reports of decreased blood flow and decreased use of glucose in this region, as summarized above. A follow-up case report described a patient who exhibited in the ^{31}P MRS spectra similar to those reported for schizophrenia well before the onset of psychotic symptoms. This finding led the investigators to propose that MRS may be of value in examining high-risk subjects, such as family members of patients with schizophrenia, for the presence of spectral abnormalities. Another group reported ^{31}P MRS results consistent with these findings. This suggests the possibility of dysfunction in the normal process of programmed synaptic pruning, critical in brain maturation. Abnormal pruning could result in neuronal loss, as well as upregulation of the postsynaptic dopaminergic receptors. These changes observed by ^{31}P clearly suggest that there should be alterations in the levels of the compounds routinely detectable by localized proton MRS.

There has been considerable interest in obtaining solvent sup-pressed proton spectra in humans. Technical advances have made it possible to relate MRS measurements to the underlying biochemistry occurring in the tissue being sampled. *N*-acetylaspartate (NAA), found by NMR in glia and

neurons but not on astrocytes, has been proposed as an index of neuronal integrity. The measurements of amino acids present in the brain have been promising. There is approximately 12 mM of glutamate (Glu) present in the brain, making it, by far, the most abundant amino acid. The rate of Glu synthesis and oxidation is different in astrocytes and neurons. Two important products of Glu metabolism are glutamine (Gln), which is formed from Glu by Glu synthetase located in astrocytes, and y-aminobutvric acid (GABA), which is an inhibitory neurotransmitter. Aspects of the metabolism of these compounds and the influence of this metabolism on MRS spectral appearance have been examined. Glu is largely confined by barriers in permeability to the tissue in which it is formed. Gln can be converted to Glu at the site of neurotransmitter activity by glutaminase, which is present in neurons. The combination of two enzymes. Gln synthetase (converts Glu to Gln) and glutaminase (converts Gln to Glu), acts as a sort of cycle to maintain the concentrations of Glu and Gln. The levels of GABA and Glu were determined by MRS in cultured preparations of cortical neurons and cerebellar granule cells. Extracts of granule cells contained large amounts of Glu, whereas the neuronal cells contained large amounts of GABA.

Detection of these compounds in vivo in clinical studies showed elevated levels of Gln in patients with chronic hepatic encephalopathy, and spectral editing methods can he applied to determine the levels of Glu in the human brain. The concentrations of Glu reported were in excellent agreement with literature values. The measurement of Glu in these studies was referenced to the concentration of the total creative present (9.6 mM) in the brain. The key feature in this methodology was the use of short echo delays (12 milliseconds) to obtain estimates of the Glu present. Thus. MRS can be used to measure the levels of these amino acids, and the levels of these compounds may provide some insights into the activity of the excitatory (Glu) and inhibitory (GABA)

neurotransmitters present in the tissue being sampled. Based on these methodological advances, studies applying spectroscopy in schizophrenia have increased.

The levels of Glu, Gln, and NAA were acquired at 4.0 tesla from 21 first-episode, neuroleptic-naive patients with schizophrenia. The Gln level was significantly higher in the left anterior cingulate cortex and thalamus of patients compared to healthy subjects, and no differences were noted for other metabolites. The findings support the role of glutamatergic activity in the pathophysiology of-schizophrenia. The lack of difference between patients and controls in the levels of NAA, a finding reported in other studies of first-episode, neuroleptic-naive patients, may relate to the brain region sampled. Regions of interest examined differ in MRS studies and have included the dorsolateral prefrontal cortex, medial temporal lobe, anterior cingulate, and thalamus. Studies that have reported lower NAA concentration in the mediodorsal region of the thalamus included chronically.treatedpatients with schizophrenia.

With growing experience and application of MRS, metabolite measures have been related to clinical variables, including symptoms and treatment. For example, in a study of 36 patients with schizophrenia, a regionally selective negative correlation was reported between prefrontal NAA to creatine ratio and negative symptoms. In a repeated-measures design, the investigators also evaluated 23 patients when stable on antipsychotics for at least 4 weeks and when off medications for at least 2 weeks. When treated, patients had higher NAA measures in the dorsolateral prefrontal cortex, suggesting a region-specific effect. To examine whether glutamatergic activity may contribute to the therapeutic effect of olanzapine (Zyprexa), Glu concentrations were measured in serum and were estimated in cingulate cortex in a within-subject design. Ten patients with schizophrenia were initially evaluated when treated with conventional neuroleptics, and the study was

repeated 8 weeks after a crossover to olanzapine. Brain Glu activity did not change significantly in the group, but concentrations increased with an improvement in negative symptoms.

MRS technology has provided estimates of brain concentrations of important cerebral metabolites, which are related to neuronal function and have been implicated in the pathophysiology of schizophrenia. Advances in magnetic field strength, data acquisition, and processing will enhance spatial and temporal resolution. Such progress, linked to other measures of cerebral function in the physiological and neurobehavioral domains, holds promise for the elucidation of pathophysiology and the understanding of therapeutics.

CHALLENGES AND FUTURE DIRECTIONS

Considerable progress with a range of neuroimaging technologies has been made in efforts to advance the understanding of the neurobiology of schizophrenia. However, the underlying mechanisms at play remain elusive. Difficulties in identifying mechanisms are endemic to disorders of complex behavior. No gene; pathological lesion; cellular, molecular, or neurochemical abnormality; or specific neural system has been recognized as being central to schizophrenia. Instead, abnormalities are evident at many levels of neurobehavioral and neurophysiological processing and in multiple neural systems—from the cerebellum to diencephalon to primary, association, and limbic cortices and the olfactory bulb. These diffuse abnormalities, which implicate neurodevelopmental aberrations, are not fully expressed as a disorder until after brain development and maturation are largely completed.

The recognition that the underlying pathological processes of schizophrenia are present throughout the CNS suggests that there may be some core defects in neurotransmission whereby the ability of neurons to respond to and process stimuli is curtailed. However, within the context of global

abnormalities, some neural systems are differentially affected. Brain regions with greater vulnerability, such as the hippocampus, prefrontal cortex, and olfactory system, are dynamic and maintain a high degree of plasticity during brain maturation and thereafter.

Both structural and functional neuroimaging studies suggest that diffuse abnormalities are evident in neuroieptic-naive, first-episode patients with schizophrenia and can be linked to neurobehavioral and neuropsychiatric manifestations. These research methods can be applied as endophenotypic measures to informative populations in genetic paradigms, such as individuals at high risk. Furthermore, evidence for progressive changes in some patients, perhaps associated with some treatments encourages longitudinal studies.

In the context of the overall effort in neurobiological research in schizophrenia, functional neuroimaging studies have contributed to advance the understanding of brain dysfunction related to neurobehavior and neuropharmacology. The field has reached some maturity in developing appropriate paradigms, and there is now a need for adequate sample size in patient and healthy populations, with attention to clinical heterogeneity and variability in brain function in relation to gender and age.

One of the major challenges in this research is the integration of neuroimaging data, across anatomical and functional measures, with clinical and neurobehavioral variables. A potential strength of functional neuroimaging is the integration of data on neuroreceptor function, metabolites, and metabolic activity. Ultimately, dysfunctional neurotransmitter systems translate to aberrant metabolism. Because CBF and metabolism reflect neuronal activity, relating these domains is prerequisite for understanding the neurobiology of schizophrenia. As new receptor subtypes are cloned and radioligands are developed and available for human studies, it will he necessary to know which neuroreceptor measures result in in-

creased neuronal activity and, in turn, how regional activation relates to behavior.

Thus, although new receptor ligands, improved resolution, and the development of methods for MR spectroscopy and flow measures are welcome and exciting, it is unlikely that the neural basis of schizophrenia will be found simply by applying the right method with sufficient resolution. Rather, it seems that the harder and longer route of understanding the interaction among the brain's structural integrity, regional activity, and neuroreceptors as they affect the clinical and neurobehavioral manifestations of schizophrenia must be undertaken.

These challenges are compounded by the absence of suitable animal models for the disorder as currently phenotypically defined, buttressing the need to identify endophenotypes that can be studied in both humans and animals. The identification of such endophenotypes in schizophrenia that have their counterparts in rodents enables investigation of the genetic, molecular, biochemical, anatomical, and physiological aspects of these behaviors. The technological developments in animal imaging will enhance the capabilities to conduct translational research. This top-down-bottom-up interchange holds great promise for advancing the understanding of the pathophysiology of schizophrenia.

SUGGESTED CROSS-REFERENCES

Functional neuroanatomy is covered in Section 1.2. The neural basis of schizophrenia psychopathology is further discussed in Section 12.7.

APPENDIX J

Constitutional and Jury Instructions Provisions Involved

United States Constitution amend. VIII:

Excessive bail shall not be required, nor excessive fines imposed, nor cruel and unusual punishments inflicted.

United States Constitution amend. XIV, Section 1:

> All persons born or naturalized in the United States, and subject to the jurisdiction thereof, are citizens of the United States and of the State wherein they reside. No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States; nor shall any State deprive any person of life, liberty, or property, without due process of law; nor deny to any person within its jurisdiction the equal protection of the laws

Michigan Model Civil Jury Instructions (Formerly The Michigan Standard Jury Instructions-Civil, Second Edition)

Volume 1

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M Civ JI 13.01 Physical Disability

One who is ill or otherwise physically disabled is required to use the same degree of care that a reasonably careful person who has the same illness or physical disability would use.

Note on Use

This instruction does not apply where voluntary intoxication or mental illness is involved. For the appropriate instructions in those cases *see* M Civ JI 13.02 and M Civ JI 13.03.

Comment

Physical handicaps and infirmities, such as blindness, deafness, short stature, a clubfoot, or the weakness of age or sex, are treated as part of the circumstances under which a reasonable person must act. Thus the standard of conduct for a blind person becomes that of a reasonable person who is blind. *Restatement (Second) of Torts* §283 C, at 18.

The same allowance is made for physical illness. Thus a heart attack or a temporary dizziness due to a fever or nausea or other similar illnesses is regarded merely as circumstances to be taken into account in determining what the reasonable person would do. *Id.*

This rule has been recognized in Michigan. *See Daniels v Clegg*, 28 Mich 32, 41 (1873); *Clemens v Sault Ste Marie*, 289 Mich 254, 256; 286 NW 232, 233-234 (1939).

The rule has been applied in the following Michigan cases: *Armstrong v Cook*, 250 Mich 180; 229 NW 433 (1930) (fainting); *Covert v Randall*, 298 Mich 38, 42; 298 NW 396, 397 (1941) (deaf mute); and *Jakubiec v Hasty*, 337 Mich 205, 212; 59 NW2d 385, 388 (1953) (deaf mute).

M Civ JI 13.03 Mental Illness-Adult

An adult who is disabled by reason of mental illness must still observe the same standard of care which a normal and reasonably careful person would exercise under the circumstances which existed in this case.

Comment

No Michigan cases have been found on this subject.

However, the general rule outside of Michigan is that unless the actor is a child, mental illness does not relieve him or her from liability for conduct which does not conform to the standards of a reasonable person under like circumstances. *Restatement (Second) of Torts* §283 B, at 16-17.

History

M Civ JI 13.03 is a revision of SJI 13.03.

Amended February 1, 1981.